FIG. 1

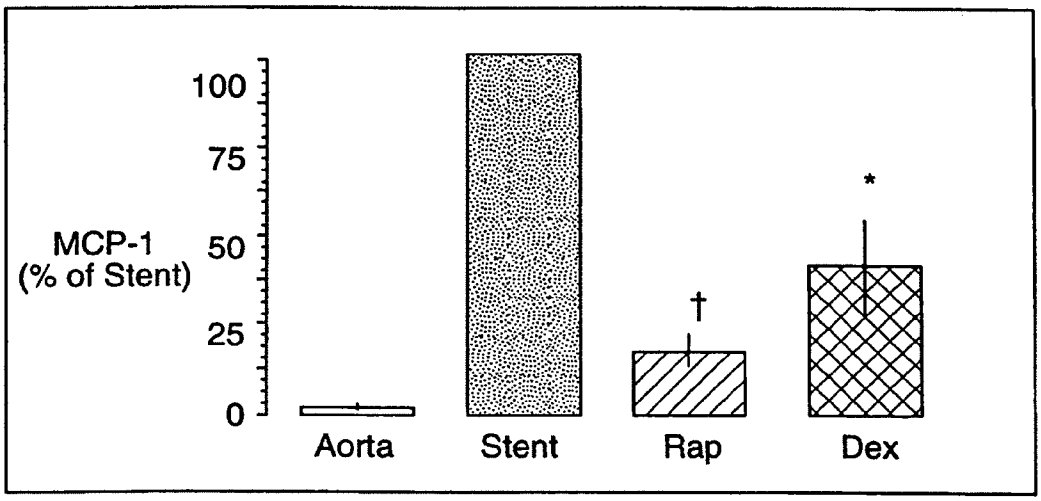


FIG. 2

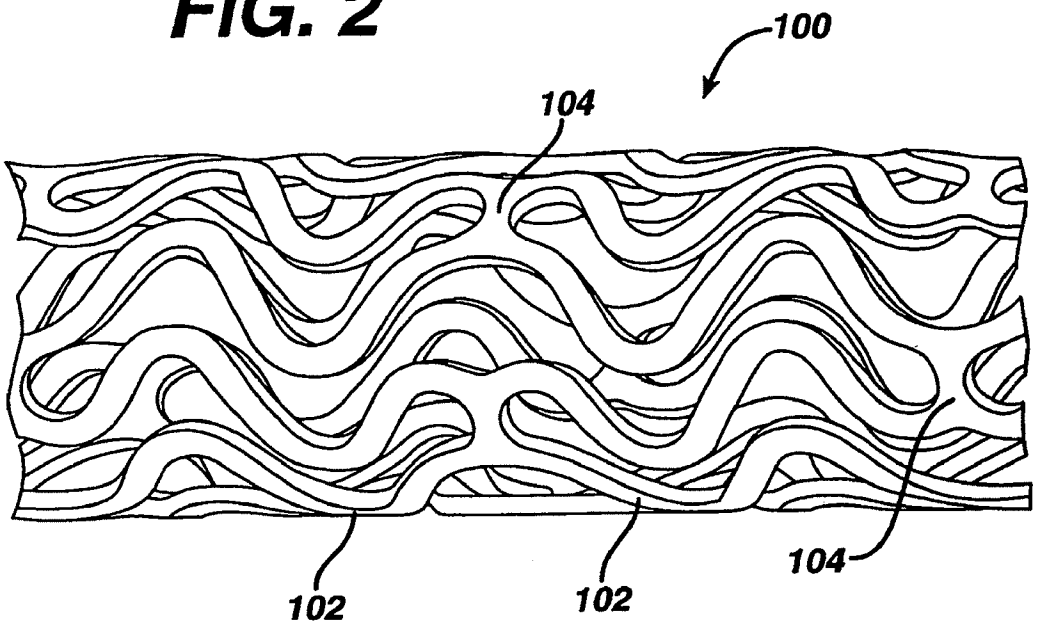
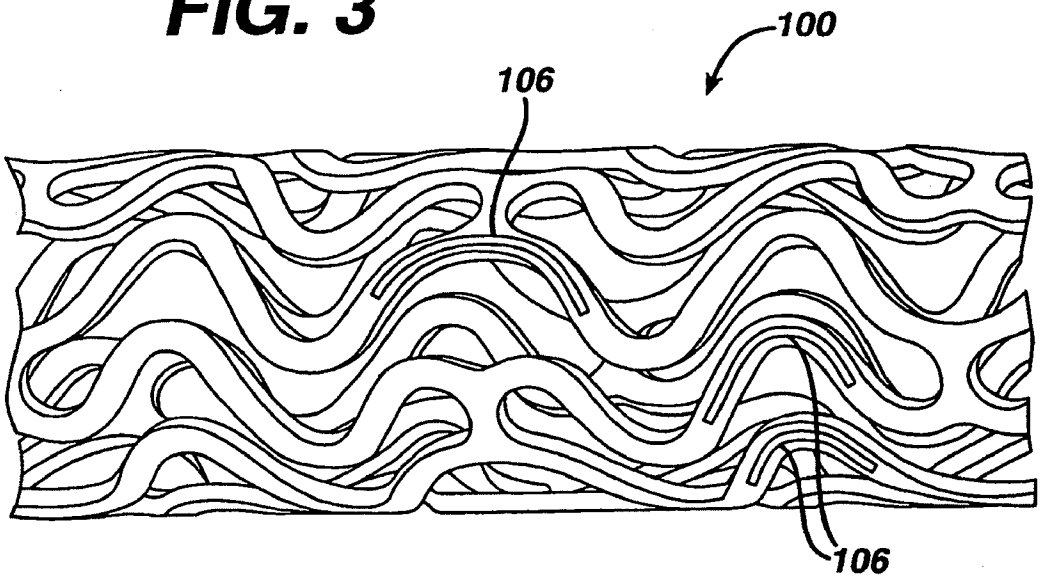


FIG. 3



DRUG/DRUG DELIVERY SYSTEMS FOR THE PREVENTION AND TREATMENT OF VASCULAR DISEASE

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Ser. No. 09/850,293, filed May 7, 2001, now abandoned, which in turn claims priority of U.S. Provisional Application No. 60/263,979, filed Jan. 25, 2001, U.S. Provisional Application No. 60/263,806, filed January 24, 2001, U.S. Provisional Application No. 60/262,614, filed Jan. 18, 2001, U.S. Provisional Application No. 60/262,461, filed Jan. 18, 2001, and is a continuation-in-part of U.S. Application No. 09,575,480, filed May 19, 2000, now pending, which in turn claims priority of U.S. Provisional Application No. 60/204,4 17, filed May 12, 2000.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to drugs and drug delivery systems for the prevention and treatment of vascular disease, and more particularly to drugs and drug delivery systems for the prevention and treatment of neointimal hyperplasia.

2. Discussion of the Related Art

Many individuals suffer from circulatory disease caused by a progressive blockage of the blood vessels that perfuse the heart and other major organs with nutrients. More severe blockage of blood vessels in such individuals often leads to hypertension, ischemic injury, stroke, or myocardial infarction. Atherosclerotic lesions, which limit or obstruct coronary blood flow, are the major cause of ischemic heart disease. Percutaneous transluminal coronary angioplasty is a medical procedure whose purpose is to increase blood flow through an artery. Percutaneous transluminal coronary angioplasty is the predominant treatment for coronary vessel stenosis. The increasing use of this procedure is attributable to its relatively high success rate and its minimal invasiveness compared with coronary bypass surgery. A limitation associated with percutaneous transluminal coronary angioplasty is the abrupt closure of the vessel which may occur immediately after the procedure and restenosis which occurs gradually following the procedure. Additionally, restenosis is a chronic problem in patients who have undergone saphenous vein bypass grafting. The mechanism of acute occlusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets and fibrin along the damaged length of the newly opened blood vessel.

Restenosis after percutaneous transluminal coronary angioplasty is a more gradual process initiated by vascular injury. Multiple processes, including thrombosis, inflammation, growth factor and cytokine release, cell proliferation, cell migration and extracellular matrix synthesis each contribute to the restenotic process.

While the exact mechanism of restenosis is not completely understood, the general aspects of the restenosis process have been identified. In the normal arterial wall, smooth muscle cells proliferate at a low rate, approximately less than 0.1 percent per day. Smooth muscle cells in the vessel walls exist in a contractile phenotype characterized by eighty to ninety percent of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, Golgi, and free ribosomes are few and are located in the perinuclear region. Extracellular matrix surrounds the smooth muscle cells and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining smooth muscle cells in the contractile phenotypic state (Campbell and Campbell, 1985).

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the vessel wall become injured, initiating a thrombotic and inflammatory response. Cell derived growth factors such as platelet derived growth factor, fibroblast growth factor, epidermal growth factor, thrombin, etc., released from platelets, invading macrophages and/or leukocytes, or directly from the smooth muscle cells provoke proliferative and migratory responses in medial smooth muscle cells. These cells undergo a change from the contractile phenotype to a synthetic phenotype characterized by only a few contractile filament bundles, extensive rough endoplasmic reticulum, Golgi and free ribosomes. Proliferation/migration usually begins within one to two days post-injury and peaks several days thereafter (Campbell and Campbell, 1987; Clowes and Schwartz, 1985).

Daughter cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate and secrete significant amounts of extracellular matrix proteins. Proliferation, migration and extracellular matrix synthesis continue until the damaged endothelial layer is repaired at which time proliferation slows within the intima, usually within seven to fourteen days post-injury. The newly formed tissue is called neointima. The further vascular narrowing that occurs over the next three to six months is due primarily to negative or constrictive remodeling.

Simultaneous with local proliferation and migration, inflammatory cells invade the site of vascular injury. Within three to seven days post-injury, inflammatory cells have migrated to the deeper layers of the vessel wall. In animal models employing either balloon injury or stent implantation, inflammatory cells may persist at the site of vascular injury for at least thirty days (Tanaka et al., 1993; Edelman et al., 1998). Inflammatory cells therefore are present and may contribute to both the acute and chronic phases of restenosis.

Numerous agents have been examined for presumed anti-proliferative actions in restenosis and have shown some activity in experimental animal models. Some of the agents which have been shown to successfully reduce the extent of intimal hyperplasia in animal models include: heparin and heparin fragments (Clowes, A. W. and Karnovsky M., Nature 265: 25-26, 1977; Guyton, J. R. et al., Circ. Res., 46: 625-634, 1980; Clowes, A. W. and Clowes, M. M., Lab. Invest. 52: 611-616, 1985; Clowes, A. W. and Clowes, M. M., Circ. Res. 58: 839-845, 1986; Majesky et al., Circ. Res. 61: 296-300, 1987; Snow et al., Am. J. Pathol. 137: 313-330, 1990; Okada, T. et al., Neurosurgery 25: 92-98, 1989), colchicine (Currier, J. W. et al., Circ. 80: 11-66, 1989), taxol (Sollot, S. J. et al., J. Clin. Invest. 95: 1869-1876, 1995), angiotensin converting enzyme (ACE) inhibitors (Powell, J. S. et al., Science, 245: 186-188, 1989), angiopeptin (Lundergan, C. F. et al. Am. J. Cardiol. 17(Suppl. B):132B-136B, 1991), cyclosporin A (Jonasson, L. et al., Proc. Natl., Acad. Sci., 85: 2303, 1988), goat-anti-rabbit PDGF antibody (Ferns, G. A. A., et al., Science 253: 1129-1132, 1991), terbinafine (Nemecek, G. M. et al., J. Pharmacol. Exp. Thera. 248: 1167-1174, 1989), trapidil (Liu, M. W. et al., Circ. 81: 1089-1093, 1990), tranilast (Fukuyama, J. et al., Eur. J. Pharmacol. 318: 327-332, 1996), interferon-gamma (Hansson, G. K. and Holm, J., Circ. 84: 1266-1272, 1991), rapamycin (Marx, S. O. et al., Circ. Res. 76: 412-417, 1995), corticosteroids (Colburn, M. D. et al., J. Vasc. Surg. 15:

510-518, 1992), see also Berk, B. C. et al., J. Am. Coll. Cardiol. 17: 111B-117B, 1991), ionizing radiation (Weinberger, J. et al., Int. J. Rad. Onc. Biol. Phys. 36: 767-775, 1996), fusion toxins (Farb, A. et al., Circ. Res. 80: 542-550, 1997) antisense oligonucleotides (Simons, M. et al., Nature 359: 67-70, 1992) and gene vectors (Chang, M. W. et al., J. Clin. Invest. 96: 2260-2268, 1995). Anti-proliferative effects on smooth muscle cells in vitro have been demonstrated for many of these agents, including heparin and heparin conjugates, taxol, tranilast, colchicine, ACE inhibitors, fusion toxins, antisense oligonucleotides, rapamycin and ionizing radiation. Thus, agents with diverse mechanisms of smooth muscle cell inhibition may have therapeutic utility in reducing intimal hyperplasia.

However, in contrast to animal models, attempts in human angioplasty patients to prevent restenosis by systemic pharmacologic means have thus far been unsuccessful. Neither aspirin-dipyridamole, ticlopidine, anti-coagulant therapy (acute heparin, chronic warfarin, hirudin or hirulog), thromboxane receptor antagonism nor steroids have been effective in preventing restenosis, although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty (Mak and Topol, 1997; Lang et al., 1991; Popma et al., 1991). The platelet GP IIb/IIIa receptor, antagonist, Reopro is still under study but has not shown promising results for the reduction in restenosis following angioplasty and stenting. Other agents, which have also been unsuccessful in the prevention of restenosis, include the calcium channel antagonists, prostacyclin mimetics, angiotensin converting enzyme inhibitors, serotonin receptor antagonists, and anti-proliferative agents. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; anti-proliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Mak and Topol, 1997; Lang et al., 1991; Popma et al., 1991).

Additional clinical trials in which the effectiveness for preventing restenosis utilizing dietary fish oil supplements or cholesterol lowering agents has been examined showing either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Mak and Topol, 1997; Franklin and Faxon, 1993: Serruys, P. W. et al., 1993). Recent observations suggest that the antilipid/antioxidant agent, probucol may be useful in preventing restenosis but this work requires confirmation (Tardif et al., 1997; Yokoi, et al., 1997). Probucol is presently not approved for use in the United States and a thirty-day pretreatment period would preclude its use in emergency angioplasty. Additionally, the application of ionizing radiation has shown significant promise in reducing or preventing restenosis after angioplasty in patients with stents (Teirstein et al., 1997). Currently, however, the most effective treatments for restenosis are repeat angioplasty, atherectomy or coronary artery bypass grafting, because no therapeutic agents currently have Food and Drug Administration approval for use for the prevention of post-angioplasty restenosis.

Unlike systemic pharmacologic therapy, stents have proven effective in significantly reducing restenosis. Typically, stents are balloon-expandable slotted metal tubes (usually, but not limited to, stainless steel), which, when expanded within the lumen of an angioplastied coronary artery, provide structural support through rigid scaffolding to the arterial wall. This support is helpful in maintaining vessel lumen patency. In two randomized clinical trials, stents increased angiographic success after percutaneous transluminal coronary angioplasty, by increasing minimal lumen diameter and reducing, but not eliminating, the incidence of restenosis at six months (Serruys et al., 1994; Fischman et al., 1994).

Additionally, the heparin coating of stents appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et al., 1996). Thus, sustained mechanical expansion of a stenosed coronary artery with a stent has been shown to provide some measure of restenosis prevention, and the coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs locally, at the site of injured tissue.

Accordingly, there exists a need for effective drugs and drug delivery systems for the effective prevention and treatment of neointimal thickening that occurs after percutaneous transluminal coronary angioplasty and stent implantation.

SUMMARY OF THE INVENTION

The drugs and drug delivery systems of the present invention provide a means for overcoming the difficulties associated with the methods and devices currently in use as briefly described above.

In accordance with one aspect, the present invention is directed to a method for the prevention of constrictive remodeling. The method comprises the controlled delivery, by release from an intraluminal medical device, of a compound in therapeutic dosage amounts.

In accordance with another aspect, the present invention is directed to a drug delivery device. The drug delivery device comprises an intraluminal medical device and a therapeutic dosage of an agent releasably affixed to the intraluminal medical device for the treatment of constrictive vascular remodeling.

The drugs and drug delivery systems of the present invention utilize a stent or graft in combination with rapamycin or other drugs/agents/compounds to prevent and treat neointimal hyperplasia, i.e. restenosis, following percutaneous transluminal coronary angioplasty and stent implantation. It has been determined that rapamycin functions to inhibit smooth muscle cell proliferation through a number of mechanisms. It has also been determined that rapamycin eluting stent coatings produce superior effects in humans, when compared to animals, with respect to the magnitude and duration of the reduction in neointimal hyperplasia. Rapamycin administration from a local delivery platform also produces an anti-inflammatory effect in the vessel wall that is distinct from and complimentary to its smooth muscle cell anti-proliferative effect. In addition, it has also been demonstrated that rapamycin inhibits constrictive vascular remodeling in humans.

Other drugs, agents or compounds which mimic certain actions of rapamycin may also be utilized in combination with local delivery systems or platforms.

The local administration of drugs, agents or compounds to stented vessels have the additional therapeutic benefit of higher tissue concentration than that which would be achievable through the systemic administration of the same drugs, agents or compounds. Other benefits include reduced systemic toxicity, single treatment, and ease of administration. An additional benefit of a local delivery device and drug, agent or compound therapy may be to reduce the dose of the therapeutic drugs, agents or compounds and thus limit their toxicity, while still achieving a reduction in restenosis.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other features and advantages of the invention will be apparent from the following, more particular description of preferred embodiments of the invention, as illustrated in the accompanying drawings.

FIG. **1** is a chart indicating the effectiveness of rapamycin as an anti-inflammatory relative to other anti-inflammatories.

FIG. **2** is a view along the length of a stent (ends not shown) prior to expansion showing the exterior surface of the stent and the characteristic banding pattern.

FIG. **3** is a perspective view of the stent of FIG. **1** having reservoirs in accordance with the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As stated above, the proliferation of vascular smooth muscle cells in response to mitogenic stimuli that are released during balloon angioplasty and stent implantation is the primary cause of neointimal hyperplasia. Excessive neointimal hyperplasia can often lead to impairment of blood flow, cardiac ischemia and the need for a repeat intervention in selected patients in high risk treatment groups. Yet repeat revascularization incurs risk of patient morbidity and mortality while adding significantly to the cost of health care. Given the widespread use of stents in interventional practice, there is a clear need for safe and effective inhibitors of neointimal hyperplasia.

Rapamycin is a macroyclic triene antibiotic produced by streptomyces hygroscopicus as disclosed in U.S. Pat. No. 3,929,992. It has been found that rapamycin inhibits the proliferation of vascular smooth muscle cells in vivo. Accordingly, rapamycin may be utilized in treating intimal smooth muscle cell hyperplasia, restenosis and vascular occlusion in a mammal, particularly following either biologically or mechanically mediated vascular injury, or under conditions that would predispose a mammal to suffering such a vascular injury. Rapamycin functions to inhibit smooth muscle cell proliferation and does not interfere with the re-endothelialization of the vessel walls.

Rapamycin functions to inhibit smooth muscle cell proliferation through a number of mechanisms. In addition, rapamycin reduces the other effects caused by vascular injury, for example, inflammation. The operation and various functions of rapamycin are described in detail below. Rapamycin as used throughout this application shall include rapamycin, rapamycin analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

Rapamycin reduces vascular hyperplasia by antagonizing smooth muscle proliferation in response to mitogenic signals that are released during angioplasty. Inhibition of growth factor and cytokine mediated smooth muscle proliferation at the late G1 phase of the cell cycle is believed to be the dominant mechanism of action of rapamycin. However, rapamycin is also known to prevent T-cell proliferation and differentiation when administered systemically. This is the basis for its immunosuppresive activity and its ability to prevent graft rejection.

The molecular events that are responsible for the actions of rapamycin, a known anti-proliferative, which acts to reduce the magnitude and duration of neointimal hyperplasia, are still being elucidated. It is known, however, that rapamycin enters cells and binds to a high-affinity cytosolic protein called FKBP12. The complex of rapamycin and

FKPB12 in turn binds to and inhibits a phosphoinositide (PI)-3 kinase called the "mammalian Target of Rapamycin" or TOR. TOR is a protein kinase that plays a key role in mediating the downstream signaling events associated with mitogenic growth factors and cytokines in smooth muscle cells and T lymphocytes. These events include phosphorylation of p27, phosphorylation of p70 s6 kinase and phosphorylation of 4BP-1, an important regulator of protein translation.

It is recognized that rapamycin reduces restenosis by inhibiting neointimal hyperplasia. However, there is evidence that rapamycin may also inhibit the other major component of restenosis, namely, negative remodeling. Remodeling is a process whose mechanism is not clearly understood but which results in shrinkage of the external elastic lamina and reduction in lumenal area over time, generally a period of approximately three to six months in humans.

Negative or constrictive vascular remodeling may be quantified angiographically as the percent diameter stenosis at the lesion site where there is no stent to obstruct the process. If late lumen loss is abolished in-lesion, it may be inferred that negative remodeling has been inhibited. Another method of determining the degree of remodeling involves measuring in-lesion external elastic lamina area using intravascular ultrasound (IVUS). Intravascular ultrasound is a technique that can image the external elastic lamina as well as the vascular lumen. Changes in the external elastic lamina proximal and distal to the stent from the post-procedural timepoint to four-month and twelve-month follow-ups are reflective of remodeling changes.

Evidence that rapamycin exerts an effect on remodeling comes from human implant studies with rapamycin coated stents showing a very low degree of restenosis in-lesion as well as in-stent. In-lesion parameters are usually measured approximately five millimeters on either side of the stent i.e. proximal and distal. Since the stent is not present to control remodeling in these zones which are still affected by balloon expansion, it may be inferred that rapamycin is preventing vascular remodeling.

The data in Table 1 below illustrate that in-lesion percent diameter stenosis remains low in the rapamycin treated groups, even at twelve months. Accordingly, these results support the hypothesis that rapamycin reduces remodeling.

TABLE 1.0

Angiographic In-Lesion Percent Diameter Stenosis (%, mean ± SD and "n=") In Patients Who Received a Rapamycin-Coated Stent

Coating Group	Post Placement	4–6 month Follow Up	12 month Follow Up
Brazil	10.6 ± 5.7 (30)	13.6 ± 8.6 (30)	22.3 ± 7.2 (15)
Netherlands	14.7 ± 8.8	22.4 ± 6.4	—

Additional evidence supporting a reduction in negative remodeling with rapamycin comes from intravascular ultrasound data that was obtained from a first-in-man clinical program as illustrated in Table 2 below.

TABLE 2.0

Matched IVUS data in Patients Who Received a Rapamycin-Coated Stent

IVUS Parameter	Post (n=)	4-Month Follow-Up (n=)	12-Month Follow-Up (n=)
Mean proximal vessel area (mm^2)	16.53 ± 3.53 (27)	16.31 ± 4.36 (28)	13.96 ± 2.26 (13)
Mean distal vessel area (mm^2)	13.12 ± 3.68 (26)	13.53 ± 4.17 (26)	12.49 ± 3.25 (14)

The data illustrated that there is minimal loss of vessel area proximally or distally which indicates that inhibition of negative remodeling has occurred in vessels treated with rapamycin-coated stents.

Other than the stent itself, there have been no effective solutions to the problem of vascular remodeling. Accordingly, rapamycin may represent a biological approach to controlling the vascular remodeling phenomenon.

It may be hypothesized that rapamycin acts to reduce negative remodeling in several ways. By specifically blocking the proliferation of fibroblasts in the vascular wall in response to injury, rapamycin may reduce the formation of vascular scar tissue. Rapamycin may also affect the translation of key proteins involved in collagen formation or metabolism.

Rapamycin used in this context includes rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

In a preferred embodiment, the rapamycin is delivered by a local delivery device to control negative remodeling of an arterial segment after balloon angioplasty as a means of reducing or preventing restenosis. While any delivery device may be utilized, it is preferred that the delivery device comprises a stent that includes a coating or sheath which elutes or releases rapamycin. The delivery system for such a device may comprise a local infusion catheter that delivers rapamycin at a rate controlled by the administrator.

Rapamycin may also be delivered systemically using an oral dosage form or a chronic injectible depot form or a patch to deliver rapamycin for a period ranging from about seven to forty-five days to achieve vascular tissue levels that are sufficient to inhibit negative remodeling. Such treatment is to be used to reduce or prevent restenosis when administered several days prior to elective angioplasty with or without a stent.

Data generated in porcine and rabbit models show that the release of rapamycin into the vascular wall from a nonerodible polymeric stent coating in a range of doses (35-430 ug/5-18 mm coronary stent) produces a peak fifty to fifty-five percent reduction in neointimal hyperplasia as set forth in Table 3 below. This reduction, which is maximal at about twenty-eight to thirty days, is typically not sustained in the range of ninety to one hundred eighty days in the porcine model as set forth in Table 4 below.

TABLE 3.0

Animal Studies with Rapamycin-coated stents. Values are mean ± Standard Error of Mean

Study	Duration	Stent[1]	Rapamycin	N	Neointimal Area (mm^2)	% Change From Polyme	% Change From Metal
Porcine							
98009	14 days	Metal		8	2.04 ± 0.17		
		1X + rapamycin	153 μg	8	1.66 ± 0.17*	-42%	-19%
		1X + TC300 + rapamycin	155 μg	8	1.51 ± 0.19*	-47%	-26%
99005	28 days	Metal		10	2.29 ± 0.21		
				9	3.91 ± 0.60**		
		1X + TC30 + rapamycin	130 μg	8	2.81 ± 0.34		+23%
		1X + TC100 + rapamycin	120 μg	9	2.62 ± 0.21		+14%
99006	28 days	Metal		12	4.57 ± 0.46		
		EVA/BMA 3X		12	5.02 ± 0.62		+10%
		1X + rapamycin	125 μg	11	2.84 ± 0.31* **	-43%	-38%
		3X + rapamycin	430 μg	12	3.06 ± 0.17* **	-39%	-33%
		3X + rapamycin	157 μg	12	2.77 ± 0.41* **	-45%	-39%
99011	28 days	Metal		11	3.09 ± 0.27		
				11	4.52 ± 0.37		
		1X + rapamycin	189 μg	14	3.05 ± 0.35		-1%
		3X + rapamycin/dex	182/363 μg	14	2.72 ± 0.71		-12%
99021	60 days	Metal		12	2.14 ± 0.25		
		1X + rapamycin	181 μg	12	2.95 ± 0.38		+38%
99034	28 days	Metal		8	5.24 ± 0.58		
		1X + rapamycin	186 μg	8	2.47 ± 0.33**		-53%
		3X + rapamycin/dex	185/369 μg	6	2.42 ± 0.64**		-54%
20001	28 days	Metal		6	1.81 ± 0.09		
		1X + rapamycin	172 μg	5	1.66 ± 0.44		-8%
20007							
	30 days	Metal		9	2.94 ± 0.43		
		1XTC + rapamycin	155 μg	10	1.40 ± 0.11*		-52%*
Rabbit							
99019	28 days	Metal		8	1.20 ± 0.07		

TABLE 3.0-continued

Animal Studies with Rapamycin-coated stents.
Values are mean ± Standard Error of Mean

Study	Duration	Stent[1]	Rapamycin	N	Neointimal Area (mm^2)	% Change From Polyme	% Change From Metal
		EVA/BMA 1X		10	1.26 ± 0.16		+5%
		1X + rapamycin	64 μg	9	0.92 ± 0.14	−27%	−23%
		1X + rapamycin	196 μg	10	0.66 ± 0.12* **	−48%	−45%
99020	28 days	Metal		12	1.18 ± 0.10		
		EVA/BMA 1X + rapamycin	197 μg	8	0.81 ± 0.16		−32%

[1]Stent nomenclature: EVA/BMA 1X, 2X, and 3X signifies approx. 500 μg, 1000 μg, and 1500 μg total mass (polymer + drug), respectively. TC, top coat of 30 μg, 100 μg, or 300 μg drug-free BMA; Biphasic; 2 × 1X layers of rapamycin in EVA/BMA spearated by a 100 μg drug-free BMA layer.
[2]0.25 mg/kg/d × 14 d preceeded by a loading dose of 0.5 mg/kg/d × 3 d prior to stent implantation.
*p < 0.05 from EVA/BMA control.
**p < 0.05 from Metal;
#Inflammation score: (0 = essentially no intimal involvement; 1 = <25% intima involved; 2 = ≧25% intima involved; 3 = >50% intima involved).

TABLE 4.0

180 day Porcine Study with Rapamycin-coated stents.
Values are mean ± Standard Error of Mean

Study	Duration	Stent[1]	Rapamycin	N	Neointimal Area (mm^2)	% Change From Polyme	% Change From Metal	Inflammation Score #
20007	3 days	Metal		10	0.38 ± 0.06			1.05 ± 0.06
(ETP-2-002233-P)		1XTC + rapamycin	155 μg	10	0.29 ± 0.03		−24%	1.08 ± 0.04
	30 days	Metal		9	2.94 ± 0.43			0.11 ± 0.08
		1XTC + rapamycin	155 μg	10	1.40 ± 0.11*		−52%*	0.25 ± 0.10
	90 days	Metal		10	3.45 ± 0.34			0.20 ± 0.08
		1XTC + rapamycin	155 μg	10	3.03 ± 0.29		−12%	0.80 ± 0.23
		1X + rapamycin	171 μg	10	2.86 ± 0.35		−17%	0.60 ± 0.23
	180 days	Metal		10	3.65 ± 0.39			0.65 ± 0.21
		1XTC + rapamycin	155 μg	10	3.34 ± 0.31		−8%	1.50 ± 0.34
		1X + rapamycin	171 μg	10	3.87 ± 0.28		+6%	1.68 ± 0.37

The release of rapamycin into the vascular wall of a human from a nonerodible polymeric stent coating provides superior results with respect to the magnitude and duration of the reduction in neointimal hyperplasia within the stent as compared to the vascular walls of animals as set forth above.

Humans implanted with a rapamycin coated stent comprising rapamycin in the same dose range as studied in animal models using the same polymeric matrix, as described above, reveal a much more profound reduction in neointimal hyperplasia than observed in animal models, based on the magnitude and duration of reduction in neointima. The human clinical response to rapamycin reveals essentially total abolition of neointimal hyperplasia inside the stent using both angiographic and intravascular ultrasound measurements. These results are sustained for at least one year as set forth in Table 5 below.

TABLE 5.0

Patients Treated (N = 45 patients) with a Rapamycin-coated Stent

Effectiveness Measures	Sirolimus FIM (N = 45 Patients, 45 Lesions)	95% Confidence Limit
Procedure Success (QCA)	100.0% (45/45)	[92.1%, 100.0%]
4-month In-Stent Diameter Stenosis (%)		
Mean ± SD (N)	4.8% ± 6.1% (30)	[2.6%, 7.0%]
Range (min, max)	(−8.2%, 14.9%)	
6-month In-Stent Diameter Stenosis (%)		
Mean ± SD (N)	8.9% ± 7.6% (13)	[4.8%, 13.0%]
Range (min, max)	(−2.9%, 20.4%)	
12-month In-Stent Diameter Stenosis (%)		
Mean ± SD (N)	8.9% ± 6.1% (15)	[5.8%, 12.0%]
Range (min, max)	(−3.0%, 22.0%)	

TABLE 5.0-continued

Patients Treated (N = 45 patients) with a Rapamycin-coated Stent		
Effectiveness Measures	Sirolimus FIM (N = 45 Patients, 45 Lesions)	95% Confidence Limit
4-month In-Stent Late Loss (mm)		
Mean ± SD (N)	0.00 ± 0.29 (30)	[−0.10, 0.10]
Range (min, max)	(−0.51, 0.45)	
6-month In-Stent Late Loss (mm)		
Mean ± SD (N)	0.25 ± 0.27 (13)	[0.10, 0.39]
Range (min, max)	(−0.51, 0.91)	
12-month In-Stent Late Loss (mm)		
Mean ± SD (N)	0.11 ± 0.36 (15)	[−0.08, 0.29]
Range (min, max)	(−0.51, 0.82)	
4-month Obstruction Volume (%) (IVUS)		
Mean ± SD (N)	10.48% ± 2.78% (28)	[9.45%, 11.51%]
Range (min, max)	(4.60%, 16.35%)	
6-month Obstruction Volume (%) (IVUS)		
Mean ± SD (N)	7.22% ± 4.60% (13)	[4.72%, 9.72%],
Range (min, max)	(3.82%, 19.88%)	
12-month Obstruction Volume (%) (IVUS)		
Mean ± SD (N)	2.11% ± 5.28% (15)	[0.00%, 4.78%],
Range (min, max)	(0.00%, 19.89%)	
6-month Target Lesion Revascularization (TLR)	0.0% (0/30)	[0.0%, 9.5%]
12-month Target Lesion Revascularization (TLR)	0.0% (0/15)	[0.0%, 18.1%]

QCA = Quantitative Coronary Angiography
SD = Standard Deviation
IVUS = Intravascular Ultrasound

Rapamycin produces an unexpected benefit in humans when delivered from a stent by causing a profound reduction in in-stent neointimal hyperplasia that is sustained for at least one year. The magnitude and duration of this benefit in humans is not predicted from animal model data. Rapamycin used in this context includes rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

These results may be due to a number of factors. For example, the greater effectiveness of rapamycin in humans is due to greater sensitivity of its mechanism(s) of action toward the pathophysiology of human vascular lesions compared to the pathophysiology of animal models of angioplasty. In addition, the combination of the dose applied to the stent and the polymer coating that controls the release of the drug is important in the effectiveness of the drug.

As stated above, rapamycin reduces vascular hyperplasia by antagonizing smooth muscle proliferation in response to mitogenic signals that are released during angioplasty injury. Also, it is known that rapamycin prevents T-cell proliferation and differentiation when administered systemically. It has also been determined that rapamycin exerts a local inflammatory effect in the vessel wall when administered from a stent in low doses for a sustained period of time (approximately two to six weeks). The local anti-inflammatory benefit is profound and unexpected. In combination with the smooth muscle anti-proliferative effect, this dual mode of action of rapamycin may be responsible for its exceptional efficacy.

Accordingly, rapamycin delivered from a local device platform, reduces neointimal hyperplasia by a combination of anti-inflammatory and smooth muscle anti-proliferative effects. Rapamycin used in this context means rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin. Local device platforms include stent coatings, stent sheaths, grafts and local drug infusion catheters or porous balloons or any other suitable means for the in situ or local delivery of drugs, agents or compounds.

The anti-inflammatory effect of rapamycin is evident in data from an experiment, illustrated in Table 6, in which rapamycin delivered from a stent was compared with dexamethasone delivered from a stent. Dexamethasone, a potent steroidal anti-inflammatory agent, was used as a reference standard. Although dexamethasone is able to reduce inflammation scores, rapamycin is far more effective than dexamethasone in reducing inflammation scores. In addition, rapamycin significantly reduces neointimal hyperplasia, unlike dexamethasone.

TABLE 6.0

Group Rapamycin Rap	N=	Neointimal Area (mm^2)	% Area Stenosis	Inflammation Score
Uncoated	8	5.24 ± 1.65	54 ± 19	0.97 ± 1.00
Dexamethasone (Dex)	8	4.31 ± 3.02	45 ± 31	0.39 ± 0.24
Rapamycin (Rap)	7	2.47 ± 0.94*	26 ± 10*	0.13 ± 0.19*
Rap + Dex	6	2.42 ± 1.58*	26 ± 18*	0.17 ± 0.30*

*= significance level $P < 0.05$

Rapamycin has also been found to reduce cytokine levels in vascular tissue when delivered from a stent. The data in FIG. 1 illustrates that rapamycin is highly effective in reducing monocyte chemotactic protein (MCP-1) levels in

the vascular wall. MCP-1 is an example of a proinflammatory/chemotactic cytokine that is elaborated during vessel injury. Reduction in MCP-1 illustrates the beneficial effect of rapamycin in reducing the expression of proinflammatory mediators and contributing to the anti-inflammatory effect of rapamycin delivered locally from a stent. It is recognized that vascular inflammation in response to injury is a major contributor to the development of neointimal hyperplasia.

Since rapamycin may be shown to inhibit local inflammatory events in the vessel it is believed that this could explain the unexpected superiority of rapamycin in inhibiting neointima.

As set forth above, rapamycin functions on a number of levels to produce such desired effects as the prevention of T-cell proliferation, the inhibition of negative remodeling, the reduction of inflammation, and the prevention of smooth muscle cell proliferation. While the exact mechanisms of these functions are not completely known, the mechanisms that have been identified may be expanded upon.

Studies with rapamycin suggest that the prevention of smooth muscle cell proliferation by blockade of the cell cycle is a valid strategy for reducing neointimal hyperplasia. Dramatic and sustained reductions in late lumen loss and neointimal plaque volume have been observed in patients receiving rapamycin delivered locally from a stent. The present invention expands upon the mechanism of rapamycin to include additional approaches to inhibit the cell cycle and reduce neointimal hyperplasia without producing toxicity.

The cell cycle is a tightly controlled biochemical cascade of events that regulate the process of cell replication. When cells are stimulated by appropriate growth factors, they move from G_0 (quiescence) to the G1 phase of the cell cycle. Selective inhibition of the cell cycle in the G1 phase, prior to DNA replication (S phase), may offer therapeutic advantages of cell preservation and viability while retaining anti-proliferative efficacy when compared to therapeutics that act later in the cell cycle i.e. at S, G2 or M phase.

Accordingly, the prevention of intimal hyperplasia in blood vessels and other conduit vessels in the body may be achieved using cell cycle inhibitors that act selectively at the G1 phase of the cell cycle. These inhibitors of the G1 phase of the cell cycle may be small molecules, peptides, proteins, oligonucleotides or DNA sequences. More specifically, these drugs or agents include inhibitors of cyclin dependent kinases (cdk's) involved with the progression of the cell cycle through the G1 phase, in particular cdk2 and cdk4.

Examples of drugs, agents or compounds that act selectively at the G1 phase of the cell cycle include small molecules such as flavopiridol and its structural analogs that have been found to inhibit cell cycle in the late G1 phase by antagonism of cyclin dependent kinases. Therapeutic agents that elevate an endogenous kinase inhibitory protein^{kip} called P27, sometimes referred to as P27^{kip1}, that selectively inhibits cyclin dependent kinases may be utilized. This includes small molecules, peptides and proteins that either block the degradation of P27 or enhance the cellular production of P27, including gene vectors that can transfact the gene to produce P27. Staurosporin and related small molecules that block the cell cycle by inhibiting protein kinases may be utilized. Protein kinase inhibitors, including the class of tyrphostins that selectively inhibit protein kinases to antagonize signal transduction in smooth muscle in response to a broad range of growth factors such as PDGF and FGF may also be utilized.

Any of the drugs, agents or compounds discussed above may be administered either systemically, for example, orally, intravenously, intramuscularly, subcutaneously, nasally or intradermally, or locally, for example, stent coating, stent covering or local delivery catheter. In addition, the drugs or agents discussed above may be formulated for fast-release or slow release with the objective of maintaining the drugs or agents in contact with target tissues for a period ranging from three days to eight weeks.

As set forth above, the complex of rapamycin and FKPB12 binds to and inhibits a phosphoinositide (PI)-3 kinase called the mammalian Target of Rapamycin or TOR. An antagonist of the catalytic activity of TOR, functioning as either an active site inhibitor or as an allosteric modulator, i.e. an indirect inhibitor that allosterically modulates, would mimic the actions of rapamycin but bypass the requirement for FKBP12. The potential advantages of a direct inhibitor of TOR include better tissue penetration and better physical/chemical stability. In addition, other potential advantages include greater selectivity and specificity of action due to the specificity of an antagonist for one of multiple isoforms of TOR that may exist in different tissues, and a potentially different spectrum of downstream effects leading to greater drug efficacy and/or safety.

The inhibitor may be a small organic molecule (approximate mw<1000), which is either a synthetic or naturally derived product. Wortmanin may be an agent which inhibits the function of this class of proteins. It may also be a peptide or an oligonucleotide sequence. The inhibitor may be administered either sytemically (orally, intravenously, intramuscularly, subcutaneously, nasally, or intradermally) or locally (stent coating, stent covering, local drug delivery catheter). For example, the inhibitor may be released into the vascular wall of a human from a nonerodible polymeric stent coating. In addition, the inhibitor may be formulated for fast-release or slow release with the objective of maintaining the rapamycin or other drug, agent or compound in contact with target tissues for a period ranging from three days to eight weeks.

As stated previously, the implantation of a coronary stent in conjunction with balloon angioplasty is highly effective in treating acute vessel closure and may reduce the risk of restenosis. Intravascular ultrasound studies (Mintz et al., 1996) suggest that coronary stenting effectively prevents vessel constriction and that most of the late luminal loss after stent implantation is due to plaque growth, probably related to neointimal hyperplasia. The late luminal loss after coronary stenting is almost two times higher than that observed after conventional balloon angioplasty. Thus, inasmuch as stents prevent at least a portion of the restenosis process, the use of drugs, agents or compounds which prevent inflammation and proliferation, or prevent proliferation by multiple mechanisms, combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

The local delivery of drugs, agents or compounds from a stent has the following advantages; namely, the prevention of vessel recoil and remodeling through the scaffolding action of the stent and the drugs, agents or compounds and the prevention of multiple components of neointimal hyperplasia. This local administration of drugs, agents or compounds to stented coronary arteries may also have additional therapeutic benefit. For example, higher tissue concentrations would be achievable than that which would occur with systemic administration, reduced systemic toxicity, and single treatment and ease of administration. An additional benefit of drug therapy may be to reduce the dose of the therapeutic compounds, thereby limiting their toxicity, while still achieving a reduction in restenosis.

There are a multiplicity of different stents that may be utilized following percutaneous transluminal coronary angioplasty. Although any number of stents may be utilized in accordance with the present invention, for simplicity, one particular stent will be described in exemplary embodiments of the present invention. The skilled artisan will recognize that any number of stents may be utilized in connection with the present invention.

A stent is commonly used as a tubular structure left inside the lumen of a duct to relieve an obstruction. Commonly, stents are inserted into the lumen in a non-expanded form and are then expanded autonomously, or with the aid of a second device in situ. A typical method of expansion occurs through the use of a catheter-mounted angioplasty balloon which is inflated within the stenosed vessel or body passageway in order to shear and disrupt the obstructions associated with the wall components of the vessel and to obtain an enlarged lumen. As set forth below, self-expanding stents may also be utilized.

FIG. **2** illustrates an exemplary stent **100** which may be utilized in accordance with an exemplary embodiment of the present invention. The expandable cylindrical stent **100** comprises a fenestrated structure for placement in a blood vessel, duct or lumen to hold the vessel, duct or lumen open, more particularly for protecting a segment of artery from restenosis after angioplasty. The stent **100** may be expanded circumferentially and maintained in an expanded configuration, that is circumferentially or radially rigid. The stent **100** is axially flexible and when flexed at a band, the stent **100** avoids any externally-protruding component parts.

The stent **100** generally comprises first and second ends with an intermediate section therebetween. The stent **100** has a longitudinal axis and comprises a plurality of longitudinally disposed bands **102**, wherein each band **102** defines a generally continuous wave along a line segment parallel to the longitudinal axis. A plurality of circumferentially arranged links **104** maintain the bands **102** in a substantially tubular structure. Essentially, each longitudinally disposed band **102** is connected at a plurality of periodic locations, by a short circumferentially arranged link **104** to an adjacent band **102**. The wave associated with each of the bands **102** has approximately the same fundamental spatial frequency in the intermediate section, and the bands **102** are so disposed that the wave associated with them are generally aligned so as to be generally in phase with one another. As illustrated in the figure, each longitudinally arranged band **102** undulates through approximately two cycles before there is a link to an adjacent band.

The stent **100** may be fabricated utilizing any number of methods. For example, the stent **100** may be fabricated from a hollow or formed stainless steel tube that may be machined using lasers, electric discharge milling, chemical etching or other means. The stent **100** is inserted into the body and placed at the desired site in an unexpanded form. In one embodiment, expansion may be effected in a blood vessel by a balloon catheter, where the final diameter of the stent **100** is a function of the diameter of the balloon catheter used.

It should be appreciated that a stent **100** in accordance with the present invention may be embodied in a shape-memory material, including, for example, an appropriate alloy of nickel and titanium. In this embodiment, after the stent **100** has been formed it may be compressed so as to occupy a space sufficiently small as to permit its insertion in a blood vessel or other tissue by insertion means, wherein the insertion means include a suitable catheter, or flexible rod. On emerging from the catheter, the stent **100** may be configured to expand into the desired configuration where the expansion is automatic or triggered by a change in pressure, temperature or electrical stimulation.

FIG. **3** illustrates an exemplary embodiment of the present invention utilizing the stent **100** illustrated in FIG. **2**. As illustrated, the stent **100** may be modified to comprise a reservoir **106**. Each of the reservoirs may be opened or closed as desired. These reservoirs **106** may be specifically designed to hold the drug, agent, compound or combinations thereof to be delivered. Regardless of the design of the stent **100**, it is preferable to have the drug, agent, compound or combinations thereof dosage applied with enough specificity and a sufficient concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the bands **102** is preferably sized to adequately apply the drug/drug combination dosage at the desired location and in the desired amount.

In an alternate exemplary embodiment, the entire inner and outer surface of the stent **100** may be coated with various drug and drug combinations in therapeutic dosage amounts. A detailed description of exemplary coating techniques is described below.

Rapamycin or any of the drugs, agents or compounds described above may be incorporated into or affixed to the stent in a number of ways and utilizing any number of biocompatible materials. In the exemplary embodiment, the rapamycin is directly incorporated into a polymeric matrix and sprayed onto the outer surface of the stent. The rapamycin elutes from the polymeric matrix over time and enters the surrounding tissue. The rapamycin preferably remains on the stent for at least three days up to approximately six months and more preferably between seven and thirty days.

Any number of non-erodible polymers may be utilized in conjunction with rapamycin. In the exemplary embodiment, the polymeric matrix comprises two layers. The base layer comprises a solution of ethylene-co-vinylacetate and polybutylmethacrylate. The rapamycin is incorporated into this layer. The outer layer comprises only polybutylmethacrylate and acts as a diffusion barrier to prevent the rapamycin from eluting too quickly and entering the surrounding tissues. The thickness of the outer layer or top coat determines the rate at which the rapamycin elutes from the matrix. Essentially, the rapamycin elutes from the matrix by diffusion through the polymer molecules. Polymers tend to move, thereby allowing solids, liquids and gases to escape therefrom. The total thickness of the polymeric matrix is in the range from about 1 micron to about 20 microns or greater. In a preferred exemplary embodiment, the base layer, including the polymer and drug, has a thickness in the range from about 8 microns to about 12 microns and the outer layer has a thickness in the range from about 1 micron to about 2 microns.

The ethylene-co-vinylacetate, polybutylmethacrylate and rapamycin solution may be incorporated into or onto the stent in a number of ways. For example, the solution may be sprayed onto the stent or the stent may be dipped into the solution. In a preferred embodiment, the solution is sprayed onto the stent and then allowed to dry. In another exemplary embodiment, the solution may be electrically charged to one polarity and the stent electrically changed to the opposite polarity. In this manner, the solution and stent will be attracted to one another. In using this type of spraying process, waste may be reduced and more control over the thickness of the coat may be achieved.

Since rapamycin works by entering the surrounding tissue, it is preferably only affixed to the surface of the stent making contact with one tissue. Typically, only the outer surface of the stent makes contact with the tissue. Accord-

ingly, in a preferred embodiment, only the outer surface of the stent is coated with rapamycin. For other drugs, agents or compounds, the entire stent may be coated.

It is important to note that different polymers may be utilized for different stents. For example, in the above-described embodiment, ethylene-co-vinylacetate and polybutylmethacrylate are utilized to form the polymeric matrix. This matrix works well with stainless steel stents. Other polymers may be utilized more effectively with stents formed from other materials, including materials that exhibit superelastic properties such as alloys of nickel and titanium.

Although shown and described is what is believed to be the most practical and preferred embodiments, it is apparent that departures from specific designs and methods described and shown will suggest themselves to those skilled in the art and may be used without departing from the spirit and scope of the invention. The present invention is not restricted to the particular constructions described and illustrated, but should be constructed to cohere with all modifications that may fall within the scope of the appended claims.

What is claimed is:

1. A drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and from about 64 μg to about 197 μg of rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating, wherein said device provides an in-stent late loss in diameter at 12 months following implantation in a human of less than about 0.5 mm, as measured by quantitative coronary angiography.

2. A drug delivery device according to claim **1** that provides an in- stent late loss in diameter at 12 months following implantation in a human of less than about 0.3 mm, as measured by quantitative coronary angiography.

3. A drug delivery device according to claim **1** or **2** that provides an in-stent diameter stenosis at 12 months following implantation in a human of less than about 22%, as measured by quantitative coronary angiography.

4. A drug delivery device according to claim **3** that provides an in-stent diameter stenosis at 12 months following implantation in a human of less than about 15%, as measured by quantitative coronary angiography.

5. A drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and from about 64 μg to about 197 μg of rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating, wherein said device provides a mean in-stent late loss in diameter in a human population at 12 months following implantation of less than about 0.5 mm, as measured by quantitative coronary angiography.

6. A drug delivery device according to claim **5** that provides a mean in-stent late loss in diameter in a human population at 12 months following implantation of less than about 0.3 mm, as measured by quantitative coronary angiography.

7. A drug delivery device according to claim **5** or **6** that provides a mean in-stent diameter stenosis in a human population at 12 months following implantation of less than about 22%, as measured by quantitative coronary angiography.

8. A drug delivery device according to claim **7** that provides a mean in-stent diameter stenosis in a human population at 12 months following implantation of less than about 15%, as measured by quantitative coronary angiography.

9. A method of inhibiting neointimal proliferation in a human coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting in the lumen of said coronary artery a drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and from about 64 μg to about 197 μg of rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating, wherein said method provides an in-stent late loss in diameter at 12 months following implantation of less than about 0.5 mm, as measured by quantitative coronary angiography.

10. A method according to claim **9** that provides an in-stent late loss in diameter at 12 months following implantation of less than about 0.3 mm, as measured by quantitative coronary angiography.

11. A method according to claim **9** or **10** that provides an in-stent diameter stenosis at 12 months following implantation of less than about 22%, as measured by quantitative coronary angiography.

12. A method according to claim **11** that provides an in-stent diameter stenosis at 12 months following implantation of less than about 15%, as measured by quantitative coronary angiography.

13. A method of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting in the lumen of said coronary artery a drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and from about 64 μg to about 197 μg of rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating, wherein said method provides a mean in-stent late loss in diameter in a human population at 12 months following implantation of less than about 0.5 mm, as measured by quantitative coronary angiography.

14. A method according to claim **13** that provides a mean in-stent late loss in diameter in a human population at 12 months following implantation of less than about 0.3 mm, as measured by quantitative coronary angiography.

15. A method according to claim **13** or **14** that provides a mean in-stent diameter stenosis in a human population at 12 months following implantation of less than about 22%, as measured by quantitative coronary angiography.

16. A method according to claim **15** that provides a mean in-stent diameter stenosis in a human population at 12 months following implantation of less than about 15%, as measured by quantitative coronary angiography.

17. The drug delivery device according to any one of claims **1**, **2**, **4** or **5** wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 64 μg to about 125 μg.

18. The drug delivery device according to to any one of claims **1**, **2**, **4** or **5** that releases a portion of said dose of rapamycin or a macrocyclic triene analog thereof at about six weeks following intraluminal implantation.

19. The drug delivery device according to any one of claims **1**, **2**, **4** or **5** wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 2 μg to about 30 μg per millimeter of stent length.

20. The drug delivery device according to claim **19** wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 3 μg to about 13 μg per millimeter of stent length.

21. The drug delivery device according to claim **19** that releases a portion of said dose of rapamycin or a macrocyclic triene analog thereof at about six weeks following intraluminal implantation.

22. The method according to any one of claims **9**, **10**, **13** or **14**, wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 64 μg to about 125 μg.

23. The method according to any one of claims **9**, **10**, **13** or **14**, wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 2 μg to about 30 μg per millimeter of stent length.

24. The method according to any one of claims **9**, **10**, **13** or **14**, wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 3 μg to about 13 μg per millimeter of stent length.

25. The method according to any one of claims **9**, **10**, **13** or **14**, wherein said drug delivery device releases a portion of said dose of rapamycin or a macrocyclic triene analog thereof at about six weeks following intraluminal implantation.

* * * * *

Multiple growth factors are released from mechanically injured vascular smooth muscle cells

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Crowley, Stephen T., Carla J. Ray, Dilsher Nawaz, Richard A. Majack, and Lawrence D. Horwitz. Multiple growth factors are released from mechanically injured vascular smooth muscle cells. *Am. J. Physiol.* 269 (*Heart Circ. Physiol.* 38): H1641–H1647, 1995.—Local release of mitogenic and chemotactic signals during angioplasty-induced vascular injury may initiate restenosis. We investigated whether mechanical injury to vascular smooth muscle cells (VSMC) results in the release of biologically active peptide growth factors. Monolayers of bovine SMC cultures were mechanically injured by cell scraping. Conditioned medium (CM) from control and injured SMC cultures was collected, and the mitogenic activity was measured by [^{3}H]thymidine incorporation in recipient SMC cultures. Mitogenic activity from injured CM was detected within 15 min after injury. When the CM from injured cells was removed 15 min after injury and replaced with serum-free media, there was no detectabe mitogenic activity in the replacement CM assessed 1–6 days postinjury. Suramin, a nonspecific peptide growth factor antagonist, significantly inhibited the mitogenic activity of injured CM. Basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF A chain), and epidermal growth factor (EGF) were detected in CM from injured cells by immunoblot analysis. The mitogenic activity of injured CM was significantly inhibited with neutralizing antibodies to bFGF (34%), PDGF-AA (32%), PDGF-BB (25%), and EGF (25%). A neutralizing antibody to tranforming growth factor (TGF)-β had no effect. In conclusion, bFGF, PDGF, and EGF are immediately released from mechanically injured VSMC. VSMC likely contain preformed, biologically active growth factors that are efficiently released from the cell cytoplasm following mechanical injury. Conditioned medium from injured VSMC is highly mitogenic, and this activity is probably due to multiple growth factors interacting synergistically.

angioplasty; restenosis; proliferation

CATHETER-BASED TECHNIQUES used to treat obstructive vascular disease invariably cause mechanically induced vessel injury. Vascular smooth muscle cells (VSMC) activation and exuberant intimal proliferation with subsequent extracellular matrix deposition are triggered in response to vascular injury and are the primary causes of restenosis following angioplasty (26, 12). The cellular signals that initiate and sustain these responses are unknown.

Local release of peptide growth factors from injured or dead VSMC has been proposed to be an early mechanism for the generation of mitogenic and chemotactic signals following vascular injury (1, 28). The importance of this mechanism is supported by previous studies which demonstrate that the degree of intimal lesion formation is proportional to the degree of vascular injury (4, 30). Thus the degree of vascular injury is an important determinant of VSMC proliferation. It has been proposed that basic fibroblast growth factor (bFGF), which lacks a signal peptide sequence necessary for cell secretion, and is abundant within the vesssel wall before injury, is the primary mitogen released by mechanically injured VSMC (17). However, VSMC are known to synthesize several other peptide growth factors, including platelet-derived growth factor (PDGF) (33), epidermal growth factor (EGF and heparin-binding EGF) (16, 32), and transforming growth factor-β (TGF-β) (21). To date, no study has clearly defined which growth factors are released from injured VSMC in sufficient quantites to stimulate growth. We hypothesized that mechanically injured SMC release multiple growth factors, which could interact synergistically at a local level to stimulate VSMC proliferation or migration early after vascular injury.

In this study, we demonstrated by immunoblot analysis and antibody neutralization studies that mechanically injured vascular VSMC immediately release the biologically active growth factors bFGF, PDGF, and EGF. Although these factors are released in small quantities, they probably interact synergistically to produce a significant mitogenic signal. Therefore, release of multiple growth factors due to mechanical injury may be an important early mitogenic stimulus for VSMC proliferation.

METHODS

Cell culture. Medial explants were dissected from freshly harvested bovine aortic strips and plated in 100-mm petri dishes (29). Aortic SMC were grown from explants in minimal essential medium (MEM) containing 10% bovine calf serum (BCS) (HyClone, Logan, UT), nonessential amino acids, 100 μg/ml penicillin, and 100 μg/ml streptomycin (Sigma Chemical, St. Louis, MO). Explant-derived cells were initially passed after pretreatment with 0.05% trypsin-0.02% EDTA (Sigma) for 5 min at 37°C. Passage 3–6 cells were used for all growth studies. The authenticity of the aortic SMC cultures was verified by immunohistochemical staining using a monoclonal antibody specific for smooth muscle actin (CGA-7) (10). Cells were subcultured into 24-well culture plates in medium containing 10% serum for 24 h at an initial density of 5×10^4 cells/well. The cells were then placed in medium containing 0.1% serum for 48 h to render them quiescent. Four replicate wells were used for each experimental condition.

Cell injury assay. Confluent cultures of quiescent VSMC grown in 24-well plates were injured by scraping the cell monolayer with a rubber policeman or cell scraper (Fisher). Each culture well was scraped in a systematic manner, in which two circumferential and three horizontal and vertical scrapes were made. By direct visualization ~80% of the cell

monolayer surface area was injured and detached from the well surface after injury. This degree of mechanical injury resulted in 25% cell death determined 24 h after injury by trypan blue staining. Disrupted, but viable, cells reattached to the culture well after 24 h. Cell injury was performed under serum-free conditions, and the conditioned medium (CM) was collected at various time points after injury. Cell debris was removed by centrifugation (2,000 rpm × 5 min at 20°C).

Growth activity assay. Equal volumes (1 ml) of injured and noninjured CM were added to separate quiescent recipient VSMC cultures (24-well plates). Other recipient cultures received an equal volume of MEM with 10% BCS, which served as maximally stimulated control cultures. Each well was pulsed with 0.5 μCi [^{3}H]thymidine at 18 h of incubation. At 24 h of incubation, the cells were rinsed twice with 1 ml of phosphate-buffered saline (PBS) and then fixed with 0.2 M perchloric acid. Wells were aspirated and rinsed again with PBS, and the acid-precipitated cellular material was solubilized with 0.3 ml 0.01 N sodium hydroxide/1.0% sodium dodecyl sulfate (SDS). The contents of each well were added to 4 ml of Ecoscint (National Diagnostics, Atlanta, GA), and radioactivity was measured with a Beckman (LS 7500; Irvine, CA) beta-scintillation counter. Incorporation of [^{3}H]thymidine into SMC DNA was expressed as counts per minute (cpm) per well.

Preparation of conditioned media for immunoblot analysis. Quiescent VSMC grown to confluence in 8–10 T 75 cm^2 flasks were mechanically injured with a plastic cell scraper in 5 ml of serum-free MEM containing 0.1% BSA and 2.5 μg/ml of the following protease inhibitors: leupeptin, aprotinin, chymostatin, pepstatin A, and antipain. The cell monolayer was completely disrupted to injure as many cells as possible (> 95% of the surface area). Medium was collected 15 min after injury, then the CM was pooled and centrifuged (1,400 *g*) for 10 min at 4°C to remove cellular debris. The CM was concentrated using a Centriprep 3 or 10 (Amicon, Beverly, MA) and centrifuged (3,000 *g*) for 4–6 h at 4°C. CM was also obtained from uninjured SMC cultures and prepared in an identical manner.

Immunoprecipitation assay. Concentrated CM samples were incubated overnight with mouse anti-bovine bFGF II monoclonal antibody (7.0 μg/ml), followed by a 2-h incubation period with protein G-agarose. Extraneous proteins were removed with three cycles of salt/detergent washes, and the agarose beads were then incubated with SDS-polyacrylamide gel electrophoresis (PAGE) sample buffer with β-mercaptoethanol for 5 min at 95°C.

Heparin-sepharose purification. Concentrated CM (5–6 ml) was incubated overnight with 0.5 ml packed heparin-Sepharose (Pharmacia). The samples were prepared in 10-ml columns and sequentially eluted with 5 ml of 0.1 M sodium acetate/0.1 M sodium chloride/10 mM 3-[(3-cholamidopropyl)-dimethylammonio]-1-propanesulfonate (CHAPS) (pH 5.0), followed by 0.1 M sodium acetate/0.1 M sodium chloride/0.16 mM CHAPS (pH 5.0), then 0.5 M tris(hydroxymethyl)aminomethane (Tris) pH 7.0/0.1 M sodium chloride, and finally with 2 ml of 0.05 M Tris (pH 7.0)/2.0 M sodium chloride. The product was concentrated with a Centricon 3 (EGF) or Centricon 10 (PDGF) to 0.1 ml and desalted with 10 mM acetic acid.

Immunoblot analysis. Concentrated and immunoprecipitated (bFGF) and heparin-sepharose purified (PDGF, EGF) CM were subjected to 15% (bFGF), 12% (PDGF), or 4–20% continuous (EGF) SDS-PAGE, and then transferred to a nitrocellulose membrane. The membrane was blocked with 5% nonfat dry milk for 1 h and then incubated with the primary antibody overnight at 4°C. bFGF was run on a reducing gel, whereas both PDGF and EGF were run under nonreducing conditions. The following primary antibodies were used: mouse anti-bovine bFGF, type II, monoclonal (Upstate Biotechnology, Lake Placid, NY); rabbit anti-human recombinant PDGF-AA and -BB polyclonal (Genzyme, Cambridge, MA); and goat anti-human recombinant EGF, polyclonal (R and D Systems, Minneapolis, MN). The blot was then washed and incubated with the horseradish peroxidase (HRP)-conjugated polyclonal secondary antibody for 1 h [bFGF: sheep anti-mouse immunoglobulin (Ig)-HRP at 1/10,000 dilution (Amersham); PDGF: donkey anti-rabbit Ig-HRP at 1/10,000 dilution (Amersham); EGF: rabbit anti-goat IgG-HRP at 1/4,000 dilution (Sigma)], and proteins were detected by ECL luminescence (Amersham).

Antibody neutralization assay. CM from injured cells was preincubated with specific neutralizing antigrowth factor antibody or mouse IgG for 2 h at 37°C, after which the treated CM was added to recipient VSMC cultures and cell proliferation determined after 24 h of incubation. The neutralizing capability and specificity of commercially obtained antibodies were verified in control experiments against each growth factor. bFGF standard with and without specific or nonspecific antibody was preincubated, but unlike PDGF or EGF, was then added directly to the recipient VSMC cultures without changing the medium. Presence of the quiescent media was necessary for the recipient cells to respond to exogenous bFGF. The anti-PDGF and anti-EGF antibodies used for immunoblot analysis also demonstrated neutralizing capability and were employed in these studies. In addition, a rabbit anti-bovine bFGF polyclonal antibody (Sigma) was used to neutralize bFGF.

Statistical analysis. Data points represent the mean value of replicate samples ± SE. One-way analysis of variance was used for multiple group comparisons, and a P value of < 0.05 using the Student-Newman-Keuls test was considered to be significant.

RESULTS

Mitogenic response of SMC to mechanical injury. At a series of time points following mechanical injury, CM was removed from cultures, and its mitogenic activity was assayed in quiescent recipient VSMC cultures. Within 5 min after mechanical injury marked mitogenic activity was observed in medium from injured cultures (Fig. 1). Injured VSMC cultures, in which the CM was removed 15 min after injury and replaced with 0.1% BCS medium, did not release significant amounts of mitogenic activity into the replacement medium during a period of 2–6 days postinjury (Fig. 2). These results indicate that SMC contain preformed, biologically active mitogens, which are released immediately following mechanical injury. Because we did not detect significant mitogenic activity in replacement CM added 15 min postinjury, it appears that mechanical injury did not induce VSMC to synthesize and secrete growth factors during the postinjury "recovery" period.

Characterization of growth activity from injured conditioned media. To initially determine whether the mitogenic activity from injured CM was due to the presence of peptide growth factors, recipient VSMC were treated with CM with or without suramin, a nonspecific peptide growth factor antagonist (24). In a concentration-responsive manner, suramin (10–500 μg/ml) significantly inhibited the mitogenic acitvity of injured CM (Fig. 3). At these concentrations, suramin

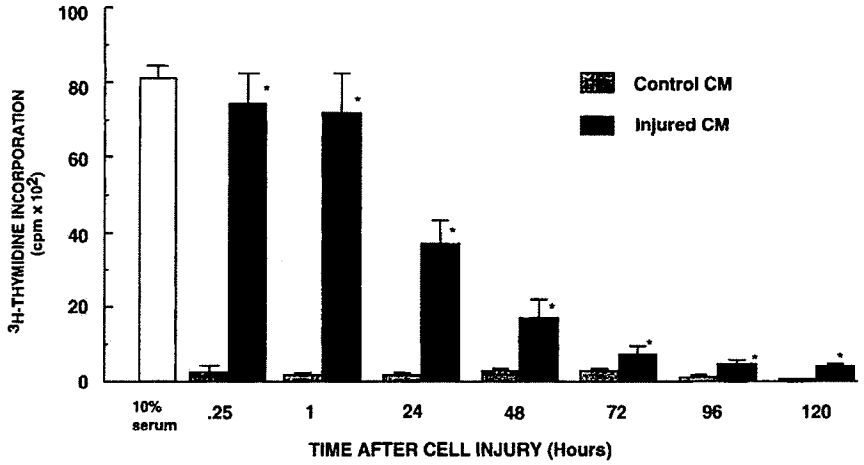

Fig. 1. Bar graph demonstrating the degree of mitogenic activity of 10% serum control and that recovered from injured and noninjured vascular smooth muscle cells (VSMC) cultures at various time points after injury. Medium was not changed after cell injury and allowed to condition for the time indicated. After centrifugation to remove cell debris, equal volumes of conditioned medium (CM) were added directly to recipient VSMC cultures. Mitogenic activity was assessed after 24 h of incubation by [^{3}H]thymidine incorporation. *Significant mitogenic effect compared with noninjured control, $n = 4$.

was not toxic to quiescent uninjured VSMC by trypan blue staining and did not induce a significant change in basal [^{3}H]thymidine incorporation or cell number.

Identification of specific growth factors from mechanically injured SMC. By immunoblot analysis immunoreactive proteins corresponding to bFGF, PDGF(AA/AB), and EGF were identified in injured CM (Figs. 4, 5, and 6). Anti-bFGF antibody recognized a 16- to 18-kDa protein corresponding to bFGF, and a second band at 32–34 kDa was also identified which may represent bFGF dimers (Fig. 4). No bands corresponding to bFGF were seen in noninjured CM or media alone. There was no cross-reactivity of the anti-bFGF antibody with samples spiked with PDGF or EGF (data not shown).

A 28-kDa protein consistent with PDGF was identified in injured CM with an anti-PDGF AA/AB antibody, which recognizes an A-chain epitope (Fig. 5). We could not detect PDGF by immunoblot with anti-PDGF BB/AB antibody (B-chain recognition) (data not shown). Therefore, we detected only PDGF-A chain from injured VSMC. Cross-reactivity of the PDGF antibodies to either bFGF or EGF by immunoblot was not observed.

A 6- to 8-kDa protein corresponding to EGF was identified in injured CM using a gradient gel (Fig. 6). This anti-EGF antibody also recognized a weak band at 19–23 kDa, which may correspond to the heparin-binding EGF (Hb-EGF) recently described as a 19- to 23-kDa protein produced by SMC and other cells (13). However, according to the manufacturer, this anti-EGF antibody does not react with Hb-EGF. EGF was not detected in uninjured control CM and cross-reactivity of the anti-EGF antibody with PDGF or bFGF was not observed.

Antibody neutralization of growth-promoting activity in conditioned media of injured SMC. Mitogenic activity from injured CM was substantially neutralized by antibodies to bFGF (34%), PDGF AA/AB (32%), PDGF BB/AB (25%), and by EGF (25%). Neutralizing antibodies to TGF-β inhibited mitogenic activity by only 9% (Fig. 7). The combination of anti-bFGF and PDGF-AA antibodies resulted in a 45% inhibition of mitogenic activity. Nonspecific immunoglobulin IgG did not inhibit VSMC proliferation in response to bFGF, PDGF, or EGF. In our cell culture system anti-PDGF A chain antibody (2–15 μg/ml) neutralized the growth effect of PDGF-AA (10 ng/ml) by 100%, anti-PDGF B chain (7–15 μg/ml) neutralized 100% of PDGF-BB stimulation (10 ng/ml), and both antibodies neutralized

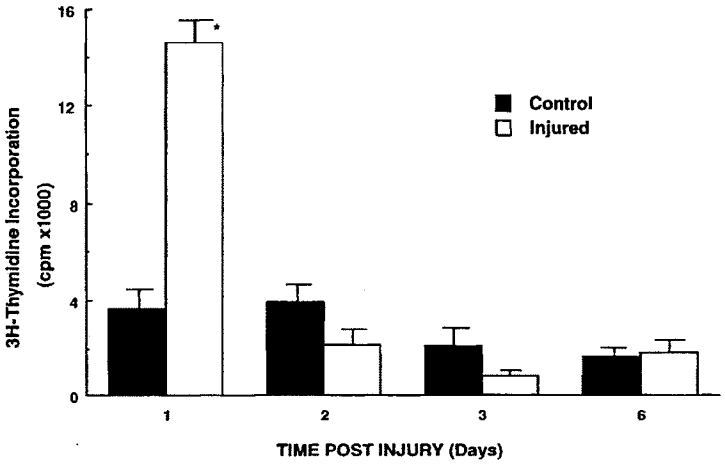

Fig. 2. Bar graph illustrating late release (1–6 days postinjury) of mitogenic activity from injured VSMC. After mechanical injury cultures were allowed to condition for 24 h, after which CM from injured and control cultures was removed and replaced by serum-free medium. At the time points indicated after this postinjury medium change, mitogenic activity of these injured cultures were assessed by [^{3}H]thymidine incorporation. *Significant mitogenic effect compared with control, $n = 4$.

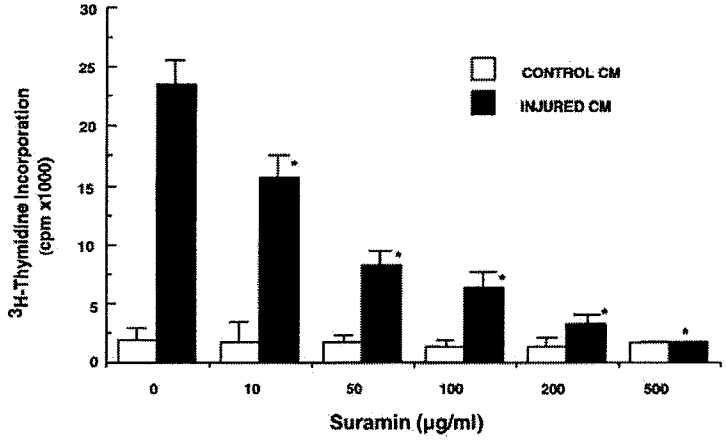

Fig. 3. Bar graph demonstrating dose-response inhibitory effect of suramin on mitogenic activity recovered from injured VSMC cultures. CM, which was recovered from injured and noninjured cultures 1 h after injury, was harvested and applied to recipient VSMC cultures in presence or absence of suramin (0–500 μg/ml). Mitogenic activity of recipient VSMC cultures was assessed at 24 h. *Significant inhibitory effect of suramin compared with untreated control, $n = 4$.

PDGF-AB stimulation by 50–80% at these concentrations. The anti-EGF antibody (10 μg/ml) neutralized EGF (5 ng/ml)-stimulated VSMC by 100%. The anti-bFGF antibody (100–150 μg/ml) neutralized 50–60% of bFGF mitogenic activity. At higher concentrations a nonspecific stimulatory effect was observed with this antibody (data not shown). According to manufacturer's information ~11% cross-reactivity is seen with the anti-PDGF antibody to PDGF A and B chains. This degree of cross-reactivity was confirmed in our culture system. Both our bFGF- and EGF-neutralizing antibodies did cross-react with PDGF (~20% of the PDGF proliferative response was reduced with these antibodies; data not shown). No significant cross-reactivity with EGF was seen with either the bFGF- or PDGF-neutralizing antibodies.

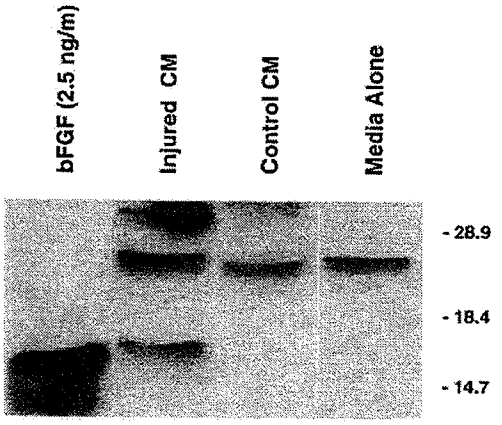

Fig. 4. Immunoblot of CM obtained from VSMC cultures probed with mouse anti-bovine basic fibroblast growth factor (bFGF) monoclonal antibody (1 μg/ml). Fifteen minutes after cell injury, CM was collected from cultures, pooled, and centrifuged to remove cell debris. CM (*lanes 2–4*) was concentrated (see METHODS) and subjected to overnight immunoprecipitation with mouse anti-bovine FGF monoclonal antibody (7.0 μg/ml). *Lane 1*: human recombinant peroxidase-bFGF standard (2.5 ng); *lane 2*: injured CM; *lane 3*: uninjured control CM; *lane 4*: uninjured CM without antibody. bFGF standard (*lane 1*) was diluted in minimal essential medium (MEM) and loaded directly on gel. Band at 24 kDa was identified as immunoglobulin light chain of immunoprecipitated antibody. Molecular sizes (kDa) are as indicated.

DISCUSSION

The main objectives in this study were to determine whether and when specific biologically active peptide growth factors are released from mechanically injured VSMC. We used cell scraping to induce mechanical injury and identified, by immunoblot analysis and antibody neutralization studies, the presence of biologically active bFGF, PDGF, and EGF, which were released into the medium after injury. The model of cell scraping used in this report has been previously employed to induce mechanical injury in endothelial cells (23, 25) and has been shown to mimic plasma membrane disruptions sustained by cells in vivo (22). Although this technique has been used to induce injury in VSMC (15), there has been no information associating mechanical injury with specific growth factor release from VSMC.

Mechanical injury induced by cell scraping resulted in immediate recovery of mitogenic activity from CM. The mitogenic activity recovered from individual cultures was comparable in degree to the growth induced by the

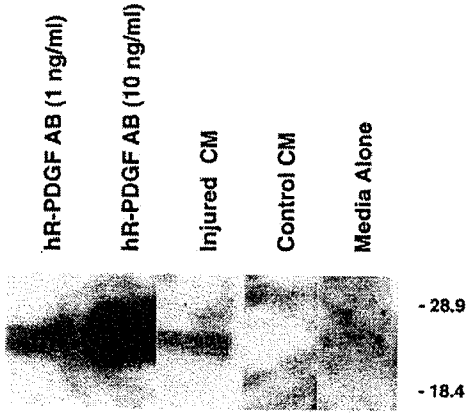

Fig. 5. Immunoblot of CM probed with rabbit anti-human recombinant (hR) PDGF(AA/AB) polyclonal antibody (10 μg/ml). Concentrated CM was heparin-Sepharose purified (see METHODS) and subjected to 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). *Lane 1:* hR-PDGF-AB (1.0 ng/ml); *lane 2*: hR-PDGF-AB (10 ng/ml); *lane 3*: injured CM; *lane 4:* control uninjured CM; *lane 5:* medium alone (MEM).

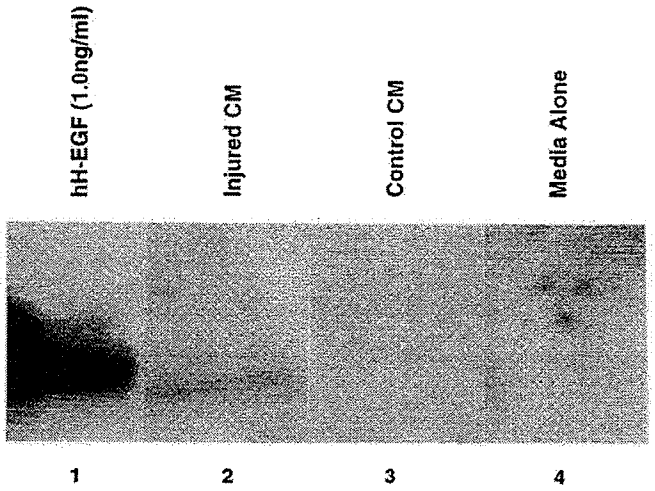

Fig. 6. Immunoblot of CM probed with goat anti-human recombinant(hH)-EGF polyclonal antibody (5 μg/ml). Concentrated CM was heparin-Sepharose purified and subjected to 4–20% gradient SDS-PAGE. *Lane 1:* hR-EGF (1.0 ng/ml; *lane 2:* injured CM; *lane 3:* control uninjured CM; *lane 4:* medium alone (MEM).

addition of 10% serum. This activity peaked within 1 h and remained detectable for days after injury. However, if the medium was removed within 15 min after injury and replaced with serum-free medium, very little additional mitogenic activity was found in media collected over the next 6 days postinjury. This suggests that VSMC contain preformed biologically active growth factors, which are quickly released into their local extracellular environment upon mechanical injury.

The rapid recovery of mitogenic activity from injured cultures of VSMC favors a cytosolic, rather than a vesicular or nuclear, location of these growth factors. Cytosolic location of bFGF in endothelial cells has previously been reported (8), and the identification of a 16- to 18-kDa bFGF band in this study is consistent with cytosolic bFGF found in other cell types (33). Matrix-bound growth factor, especially bFGF, could potentially be an alternative source of mitogenic activity following mechanical injury. However, in our model VSMC were injured after 48 h in culture, when matrix deposition of bFGF is minimal compared with the amount of bFGF detectable intracellularly (31). Furthermore, Linder et al. (17) demonstrated predominantly cytoplasmic bFGF with some nuclear localization of bFGF within VSMC of uninjured rat carotid arteries by immunocytochemical staining. Although it is probable that injury-induced growth factor release did occur from matrix sites, it is more likely that much of the release occurred from a cytosolic source given the abundant presence of growth factor within cultured VSMC (31).

By immunoblot analysis we detected PDGF-A chain and not PDGF-B chain in CM from injured VSMC. PDGF-A chain is the predominant PDGF isoform produced by VSMC in vivo (20), but all isoforms have mitogenic and chemotactic effects on VSMC. We did observe a significant reduction in the mitogenic activity of injured CM with neutralizing anti-PDGF BB/AB antibody. Therefore, BB isoform, which may have been

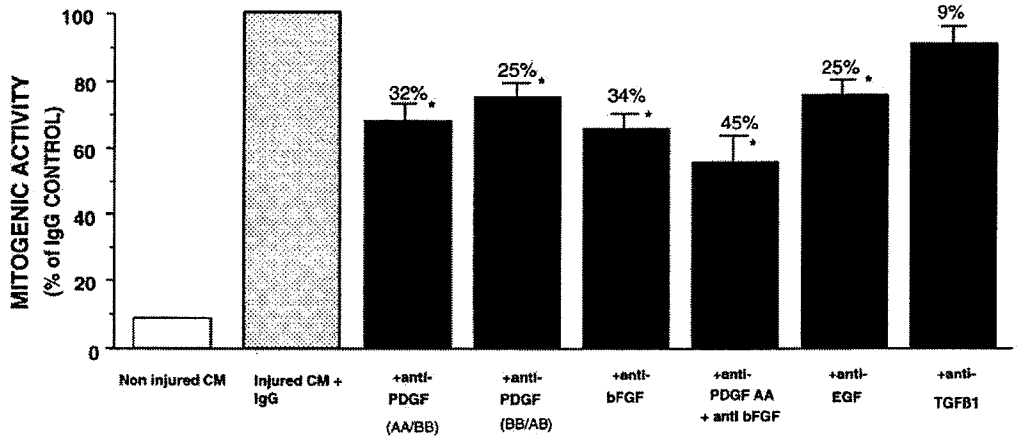

Fig. 7. Bar graph showing anti-growth factor antibody neutralization of injured CM. Degree of mitogenic inhibition is expressed as a percentage of immunoglobulin (Ig) G-treated injured CM control. CM was preincubated with specific neutralizing antibody: anti-bFGF (150 μg/ml), anti-PDGF A or B chain (15 μg/ml), anti-EGF (10 μg/ml), or mouse IgG for 2 h at 37°C and then added to recipient VSMC cultures. *Significant neutralizing effect compared with CM control treated with nonspecific IgG. Mitogenic activity was assessed at 24 h, $n = 3$.

present at a concentration below the threshold which we could detect by immunoblot analysis, could be contributing to the mitogenic activity of injured CM. However, since the anti-PDGF neutralizing antibodies used in our study displayed some cross-reactivity between PDGF-A and -B chains and with bFGF, we cannot confirm the presence of PDGF-BB isoform in injured CM. Likewise, it was not possible to accurately determine the relative contribution of each growth factor to the total mitogenic activity released by injured VSMC.

Because VSMC can both produce and respond to bFGF, PDGF, and EGF, these factors may work in concert to mediate initial responses to injury. It is well known that peptide growth factors interact synergistically to markedly enhance cell proliferation (7, 14). In addition, bFGF with its potential ability to regulate matrix proteins and plasminogen activators (2), may help facilitate the promigratory effect of PDGF and EGF. PDGF, in the setting of tissue injury, could act as a multifunctional protein, since it can increase the release of collagenase by fibroblasts (3) and induce chemoattracted macrophages and fibroblasts to synthesize TGF-β (27). PDGF, EGF, and bFGF all have been strongly implicated in wound repair responses in nonvascular tissues (5, 11, 19) and have been shown to accelerate wound healing in other models (6). A specific antibody to PDGF has been demonstrated to inhibit VSMC replication after arterial injury (9), and an anti-bFGF antibody treatment has been shown to partially limit neointimal formation in a rat model (18). However, further investigation is needed to define the functional role these factors play in mediating vascular responses to injury.

Results from our study indicate that upon injury, VSMC release multiple growth factors, which include bFGF, PDGF, and EGF. Therefore, attempting to inhibit only one such factor is unlikely to significantly attenuate subsequent intimal lesion formation. These growth factors are each released in small quantities and probably interact synergistically to produce a strong mitogenic signal. Although we cannot exclude a role for other growth factors, local release of bFGF, PDGF, and EGF by injured VSMC following mechanical injury may provide an important early mitogenic stimulus after vascular injury.

The authors thank Drs. Philip E. Schwartz and Kim A. Marcom for helpful suggestions.

This study was supported by the American Heart Association, Colorado Affiliate, by Grant HL-48177 from the National Heart, Lung, and Blood Institute, and by the Colorado Foundation for Biomedical Education and Research.

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Received 26 October 1994; accepted in final form 11 May 1995.

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Library of Congress Cataloging in Publication Data
Main entry under title:

Merriam-Webster's collegiate dictionary. — 10th ed.
p. cm.
Includes index.
ISBN 0-87779-708-0 (unindexed). — ISBN 0-87779-709-9 (indexed).
— ISBN 0-87779-710-2 (deluxe). — ISBN 0-87779-707-2 (laminated cover).
1. English language—Dictionaries. I. Merriam-Webster, Inc.
PE1628.M36 1993
423—dc20 93-20206
CIP

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hys·ter·ics \-ˈter-iks\ *n pl but sing or pl in constr* (1721) : a fit of uncontrollable laughter or crying

hys·ter·oid \ˈhis-tə-ˌrȯid\ *adj* (ca. 1855) : resembling or tending toward hysteria

hys·ter·on prot·er·on \ˌhis-tə-ˌrän-ˈprä-tə-ˌrän, -tə-rən-ˈprä-tə-rən, -ˈprō-\ *n* [LL, fr. Gk, lit., (the) later earlier, (the) latter first] (1565) : a figure of speech consisting of the reversal of a natural or rational order (as in "then came the thunder and the lightning")

hys·ter·ot·o·my \ˌhis-tə-ˈrä-tə-mē\ *n, pl* **-mies** [NL *hysterotomia*, fr. *hyster-* + *-tomia* -tomy] (1801) : surgical incision of the uterus; *esp* : CESAREAN SECTION

I

i \ˈī\ *n, pl* **i's** *or* **is** \ˈīz\ *often cap, often attrib* (bef. 12c) **1 a** : the 9th letter of the English alphabet **b** : a graphic representation of this letter **c** : a speech counterpart of orthographic *i* **2** : ONE — see NUMBER table **3** : a graphic device for reproducing the letter *i* **4** : one designated *i* esp. as the 9th in order or class **5** : something shaped like the letter I **6** : a unit vector parallel to the x-axis **7** [abbr. for *incomplete*] **a** : a grade rating a student's work as incomplete **b** : one graded or rated with an I **8** : I FORMATION

[1]**I** \ˈī, ə\ *pron* [ME, fr. OE *ic*; akin to OHG *ih* I, L *ego*, Gk *egō*] (bef. 12c) : the one who is speaking or writing ⟨~ feel fine⟩ — compare ME, MINE, MY, WE ***usage*** see ME

[2]**I** \ˈī\ *n, pl* **I's** *or* **Is** \ˈīz\ (1539) : someone aware of possessing a personal individuality : SELF

-i- [ME, fr. OF, fr. L, thematic vowel of most nouns and adjectives in combination] — used as a connective vowel to join word elements esp. of Latin origin ⟨matr*i*lineal⟩ ⟨rat*i*cide⟩

[1]**-ia** *n suffix* [NL, fr. L & Gk, suffix forming feminine nouns] **1** : pathological condition ⟨hyster*ia*⟩ **2** : genus of plants or animals ⟨Fuchs*ia*⟩ **3** : territory : world : society ⟨suburb*ia*⟩

[2]**-ia** *n pl suffix* [NL, fr. L (neut. pl. of *-ius*, adj. ending) & Gk, neut. pl. of *-ios*, adj. ending] **1** : higher taxon (as class or order) consisting of (such plants or animals) ⟨Saur*ia*⟩ **2** : things derived from or relating to (something specified) ⟨militar*ia*⟩

[3]**-ia** *pl of* -IUM

Ia·go \ē-ˈä-(ˌ)gō\ *n* : the villain of Shakespeare's tragedy *Othello*

-ial *adj suffix* [ME, fr. MF, fr. L *-ialis*, fr. *-i-* + *-alis* -al] : [1]-AL ⟨manor*ial*⟩

iamb \ˈī-ˌam(b)\ *or* **iam·bus** \ī-ˈam-bəs\ *n, pl* **iambs** \ˈī-ˌamz\ *or* **iam·bus·es** [L *iambus*, fr. Gk *iambos*] (1586) : a metrical foot consisting of one short syllable followed by one long syllable or of one unstressed syllable followed by one stressed syllable (as in *above*) — **iam·bic** \ī-ˈam-bik\ *adj or n*

-ian — see -AN

-iana — see -ANA

-iasis *n suffix, pl* **-iases** [NL, fr. L, fr. Gk, suffix of action, fr. denominative verbs in *-ian*, *-iazein*] : disease having characteristics of or produced by (something specified) ⟨onchocerc*iasis*⟩ ⟨ancylostom*iasis*⟩

-iatric *also* **-iatrical** *adj comb form* [NL *-iatria*] : of or relating to (such) medical treatment or healing ⟨ped*iatric*⟩

-iatrics *n pl comb form but sing or pl in constr* : medical treatment ⟨ped*iatrics*⟩

iat·ro·gen·ic \(ˌ)ī-ˌa-trə-ˈje-nik\ *adj* [Gk *iatros* physician + E *-genic*] (1924) : induced inadvertently by a physician or surgeon or by medical treatment or diagnostic procedures ⟨an ~ rash⟩ — **iat·ro·gen·i·cal·ly** \-ˈje-ni-k(ə-)lē\ *adv*

-iatry *n comb form* [F *-iatrie*, fr. NL *-iatria*, fr. Gk *iatreia* art of healing, fr. *iatros* healer, fr. *iasthai* to heal] : medical treatment : healing ⟨pod*iatry*⟩

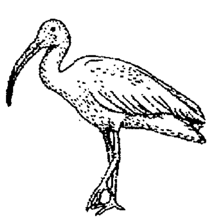
I band \ˈī-\ *n* (1948) : an isotropic band of a striated muscle fiber

I beam *n* (ca. 1889) : an iron or steel beam that is I-shaped in cross section

[1]**Ibe·ri·an** \ī-ˈbir-ē-ən\ *n* [*Iberia*, ancient region of the Caucasus] (1601) : a member of one or more peoples anciently inhabiting the Caucasus in Asia between the Black and Caspian seas — **Iberian** *adj*

[2]**Iberian** *n* [*Iberia*, peninsula in Europe] (1611) **1 a** : a member of one or more peoples anciently inhabiting parts of the peninsula comprising Spain and Portugal **b** : a native or inhabitant of Spain or Portugal or the Basque region **2** : one or more of the languages of the ancient Iberians — **Iberian** *adj*

ibex \ˈī-ˌbeks\ *n, pl* **ibex** *or* **ibex·es** [L] (1607) : any of several wild goats (genus *Capra*, esp. *C. ibex*) living chiefly in high mountain areas of the Old World and having large recurved horns transversely ridged in front



ibis

ibi·dem \ˈi-bə-ˌdem; i-ˈbī-dəm, -ˈbē-\ *adv* [L] (ca. 1771) : in the same place

-ibility — see -ABILITY

ibis \ˈī-bəs\ *n, pl* **ibis** *or* **ibis·es** [ME, fr. L, fr. Gk, fr. Egypt *hb*] (14c) : any of various wading birds (family Threskiornithidae) related to the herons but distinguished by a long slender downwardly curved bill

Ibi·zan hound \i-ˈbē-zən-\ *n* [*Ibiza* Island] (1960) : any of a breed of slender agile medium-sized hunting dogs developed in the Balearic Islands with a short and smooth or a wire-haired coat

-ible — see -ABLE

Ibo \ˈē-(ˌ)bō\ *n, pl* **Ibo** *or* **Ibos** (1732) **1** : a member of a people of the area around the lower Niger in Africa **2** : the language of the Ibo people

Ib·sen·ism \ˈib-sə-ˌni-zəm, ˈip-\ *n* (1890) **1** : dramatic invention or construction characteristic of Ibsen **2** : championship of Ibsen's plays and ideas — **Ib·sen·ite** \-ˌnīt\ *n or adj*

ibu·pro·fen \ˌī-byu̇-ˈprō-fən *also* ī-ˈbyü-prə-fən\ *n* [*is-* + *butyl* + *propionic acid* + *-fen* (alter. of *phenyl*)] (1969) : a nonsteroidal anti-inflammatory drug $C_{13}H_{18}O_2$ used to relieve pain and fever

[1]**IC** \ˌī-ˈsē\ *n* (1947) : IMMEDIATE CONSTITUENT

[2]**IC** *n* (1966) : INTEGRATED CIRCUIT

[1]**-ic** *adj suffix* [ME, fr. OF & L; OF *-ique*, fr. L *-icus* — more at -Y] **1** : having the character or form of : being ⟨panoram*ic*⟩ : consisting of ⟨run*ic*⟩ **2 a** : of or relating to ⟨alderman*ic*⟩ **b** : related to, derived from, or containing ⟨alcohol*ic*⟩ **3** : in the manner of : like that of : characteristic of ⟨Byron*ic*⟩ **4** : associated or dealing with ⟨Ved*ic*⟩ : utilizing ⟨electron*ic*⟩ **5** : characterized by : exhibiting ⟨nostalg*ic*⟩ : affected with ⟨allerg*ic*⟩ **6** : caused by ⟨amoeb*ic*⟩ **7** : tending to produce ⟨analges*ic*⟩ **8** : having a valence relatively higher than in compounds or ions named with an adjective ending in *-ous* ⟨ferr*ic* iron⟩

[2]**-ic** *n suffix* : one having the character or nature of : one belonging to or associated with : one exhibiting or affected by : one that produces

-ical *adj suffix* [ME, fr. LL *-icalis* (as in *clericalis* clerical, *radicalis* radical)] : -IC ⟨symmetr*ical*⟩ ⟨geolog*ical*⟩ — sometimes differing from *-ic* in that adjectives formed with *-ical* have a wider or more transferred semantic range than corresponding adjectives in *-ic*

Ic·a·rus \ˈi-kə-rəs\ *n* [L, fr. Gk *Ikaros*] : the son of Daedalus who to escape imprisonment flies by means of artificial wings but falls into the sea and drowns when the wax of his wings melts as he flies too near the sun

ICBM \ˌī-ˌsē-(ˌ)bē-ˈem\ *n, pl* **ICBM's** *or* **ICBMs** \-ˈemz\ (1955) : an intercontinental ballistic missile

[1]**ice** \ˈīs\ *n, often attrib* [ME *is*, fr. OE *īs*; akin to OHG *īs* ice, Av *isu-* icy] (bef. 12c) **1 a** : frozen water **b** : a sheet or stretch of ice **2** : a substance resembling ice; *esp* : the solid state of a substance usu. found as a gas or liquid ⟨ammonia ~ in the rings of Saturn⟩ **3** : a state of coldness (as from formality or reserve) **4 a** : a frozen dessert containing a flavoring (as fruit juice); *esp* : one containing no milk or cream **b** *Brit* : a serving of ice cream **5** *slang* : DIAMONDS; *broadly* : JEWELRY **6** : an undercover premium paid to a theater employee for choice theater tickets — **ice·less** \ˈī-sləs\ *adj* — **on ice 1** : with every likelihood of being won or accomplished **2** : in reserve or safekeeping

[2]**ice** *vb* **iced; ic·ing** *vt* (15c) **1 a** : to coat with or convert into ice **b** : to chill with ice **c** : to supply with ice **2** : to cover with or as if with icing **3** : to put on ice **4** : SECURE 1b ⟨made two free throws . . . to ~ the win —Jack McCallum⟩ **5** : to shoot (an ice hockey puck) the length of the rink and beyond the opponents' goal line **6** *slang* : KILL 1a ~ *vi* **1** : to become ice-cold **2 a** : to become covered with ice — often used with *up* or *over* **b** : to have ice form inside ⟨the carburetor *iced* up⟩

ice age *n* (1873) **1** : a time of widespread glaciation **2** *cap I&A* : the Pleistocene glacial epoch

ice ax *n* (1820) : a combination pick and adze with a spiked handle that is used in mountain climbing

ice bag *n* (1883) : a waterproof bag to hold ice for local application of cold to the body

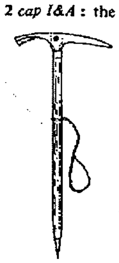
ice·berg \ˈīs-ˌbərg\ *n* [prob. part trans. of Dan or Norw *isberg*, fr. *is* ice + *berg* mountain] (1820) **1** : a large floating mass of ice detached from a glacier **2** : an emotionally cold person **3** : ICEBERG LETTUCE

iceberg lettuce *n* (1893) : any of various crisp light green lettuces that when mature have the leaves arranged in a compact head

ice·blink \-ˌbliŋk\ *n* (1817) : a glare in the sky over an ice field

ice·boat \-ˌbōt\ *n* (ca. 1819) : a skeleton boat or frame on runners propelled on ice usu. by sails

ice·boat·ing \-ˌbō-tiŋ\ *n* (1885) : the sport of sailing in iceboats — **ice·boat·er** \-ˌbō-tər\ *n*



ice ax

Webster's Third New International Dictionary

OF THE ENGLISH LANGUAGE UNABRIDGED

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MERRIAM-WEBSTER INC., *Publishers*
SPRINGFIELD, MASSACHUSETTS, U.S.A.

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Library of Congress Cataloging in Publication Data
Main entry under title:

Webster's third new international dictionary of the English language, unabridged: a Merriam-Webster/editor in chief, Philip Babcock Gove and the Merriam-Webster editorial staff.
p. cm.
ISBN 0-87779-201-1

1. English language—Dictionaries. I. Gove, Philip Babcock, 1902–1972. II. Merriam-Webster, Inc.
PE1625.W36 1993
423–dc20 93-10630
CIP

MADE IN THE UNITED STATES OF AMERICA
484950QPH9796

bar·som \'bärsəm\ *n* -s [Per *barsam*, fr. MPer *barsum*, fr. Av *barəsman*; akin to Skt *barhis* sacrificial grass, *bṛhati* he plucks] : a bundle of sacred twigs or metal rods used by priests in Zoroastrian ceremonies

bar spade *n* [¹*bar*] : a trenching spade with a cutting blade welded across the ends of three parallel bars for use in spading wet sticky soil

bar·spoon \'ˌ\ *n* [¹*bar* (counter) + *spoon*] : a spoon equivalent to a teaspoon that is used in measuring ingredients for mixed drinks

bar·stool \'ˌ\ *n* [¹*bar* (counter) + *stool*] : a high stool that usu. has a round seat fixed permanently on a central post

bart \'bärt, 'bät\ *n* -s *often cap* [by abbr.] : BARONET

bar tack *n* [¹*bar*] : a reinforcement for points of strain in clothing consisting of a bar-shaped line of small stitches worked across several threads — **bartacked** \'ˌ\ *adj*

bar-tailed godwit \'ˌ-\ *n* : a godwit (*Limosa lapponica*) that has a slightly curved bill, a closely barred tail, and relatively short legs and that breeds in extreme northern Europe and Asia and winters chiefly in Africa and Australasia

bar·tangi \bär'tänē\ *n, pl* **bartangi** *or* **bartangis** *usu cap* [fr. the *Bartang* river valley, Tadzhik S.S.R., U.S.S.R.] **1** : an Iranian people from the Bartang river valley in the western Pamirs **2** : a member of the Bartangi people

bar·tend \'bär,tend, 'bä,-\ *vi* -ED/-ING/-S [back-formation fr. *bartender*] : to act as a bartender esp. professionally

bar·tend·er \-ə(r)\ *n* -s [¹*bar* (counter) + *tender*] : one that serves alcoholic beverages at a bar : BARKEEPER

[1]**bar·ter** \'bärd-ər, 'bä\,]tə(r)\ *vb* **bartered; bartered; bartering** \]d-əriŋ,]tariŋ *also*]-triŋ\ **barters** [ME *bartren*, fr. MF *barater* to cheat, exchange] *vi* **1** : to trade by exchanging one commodity for another (~*ed* for furs with tobacco and rum) : TRUCK (stores ~*ing* with farmers) **2** : to trade in intangible or nonmaterial values (~ for success at the price of happiness) ~ *vt* **1** : to trade or exchange by bartering (Indians . . . ~*ed* their services for "ironmongery" —C.B.Hitchcock) **2** : to trade or exchange (as an ideal or intangible value) for a material or unworthy consideration — often used with *away* (would cheerfully ~ away all the social gains of the last century for one first-class new symphony —Hunter Mead)

[2]**barter** \"\ *n* -s **1** : the act or practice of carrying on trade by bartering : an exchange of goods for goods (the former system of ~ has virtually ceased to exist, replaced by money economy —H.S.Tschopik) **2** : the thing given in exchange in bartering (the trinkets were ~ for food and manual service from the natives)

[1]**barth·ian** \'bärd-ēən, -rthē-\ *adj, usu cap* [Karl *Barth* †1968 Swiss theologian + E *-ian*] : of or relating to Barth or to his theology which has exercised a formative influence in the development of the neoorthodox school of Protestant theology

[2]**barthian** \"\ *n* -s *usu cap* : a follower or adherent of the theology of Karl Barth

barth·ian·ism \-,nizəm\ *n* -s *usu cap* : the Barthian crisis theology or dialectical theology that rejects theological liberalism and its emphasis on empirical methods and stresses instead reliance on supernatural revelation

barth·ite \'bär,thīt, -rd-,īt\ *n* -s [G *barthit*, fr. *Barth*, 20th cent. mining engineer in southwestern Africa + G *-it* -ite] : CONICHALCITE

bar·tho·lin·itis \,bärthələ'nīd-əs, -rt°l-\ *n, pl* **bartholin·itides** \-ī,tēz\ *sometimes cap* [NL, fr. ISV (glands of) *Bartholin* + NL *-itis*] : inflammation of the glands of Bartholin

bartholin's gland *n, usu cap B* : GLAND OF BARTHOLIN

bar·ti·zan \'bärd-əzən, ˌ-ˌ'zan\ *n* -s [alter. of ME *bretasynge*, fr. *bretasce* parapet — more at BRATTICE] : a small structure (as a turret) overhanging or projecting from a building near an entrance for lookout or defense or for support for a flagpole — **bar·ti·zaned** \-nd\ *adj*


bartizans

bar·ton \'bärt°n\ *n* -s [ME *berton*, fr. OE *beretūn* threshing floor, barn, fr. *bere* barley + *tūn* enclosure — more at BARLEY, TOWN] **1** *dial Eng* : a large farm; *esp* : a demesne farm or the demesne lands of a manor **2** *dial Eng* **a** : a farmyard or the outbuildings behind a farmhouse **b** : a poultry yard or hen coop

bar·ton·el·la \,bärt°n'elə\ *n* [NL, fr. A.L.*Barton* †1909 Peruvian physician + NL *-ella*] **1** *cap* : the type genus of Bartonellaceae including the causative organism of Oroya fever and verruga peruana in man **2** -s *sometimes cap* : any member of the genus *Bartonella*

bar·ton·el·la·ce·ae \,bärt°n,e'lāsē,ē\ *n pl, cap* [NL, fr. *Bartonella*, type genus + *-aceae*] : a family of microorganisms (order Rickettsiales) that invade blood and tissue cells of man and other vertebrates and are often transmitted by bloodsucking arthropods

bar·ton·el·lo·sis \-'lōsəs\ *n, pl* **bartonello·ses** \-ō,sēz\ *sometimes cap* [NL, fr. *Bartonella* + *-osis*] : a disease of man and other mammals orig. in the valleys of the Andes of Peru but now in other parts of So. America characterized by severe anemia and high fever followed by an eruption like warts on the skin and caused by an organism (*Bartonella bacilliformis*) like rickettsia that invades the red blood cells and is transmitted by sandflies (genus *Phlebotomus*)

[1]**bar·to·nia** \bär'tōnēə\ [NL, fr. Benjamin S. *Barton* †1815 Amer. botanist + NL *-ia*] *syn of* MENTZELIA

[2]**bartonia** \"\ *n* [NL, fr. B.S.*Barton* + NL *-ia*] **1** -s : MENTZELIA 2a **2** *cap* : a genus of very small herbs (family Gentianaceae) with scalelike leaves and small yellow flowers

bar tracery *n* [¹*bar*] : decorative architectural tracery that is formed by the curves and intersections of the molded bars of mullions

bar·tra·mia \bär'trāmēə\ *n, cap* [NL, fr. William *Bartram* †1823 Am. naturalist + NL *-ia*] : a genus (the type of the family Bartramiaceae) of acrocarpous mosses with globular capsules which dry in ridges and folds

bar·tra·mi·an sandpiper *or* **bartramian plover** \(')bär¦trāmēən-\ *n, usu cap B* [William *Bartram* + E *-ian*] : UPLAND PLOVER

bar·tram oak \'bärtrəm-\ *n, usu cap B* [after John *Bartram* †1777 Am. botanist] : an oak (*Quercus heterophylla*) of the eastern U.S. usu. considered a natural hybrid between the northern red oak and the willow oak

bartram's sandpiper *n, usu cap B* [after William *Bartram*] : UPLAND PLOVER

bartree \'ˌ\ *n* -s [¹*bar* + *tree*] : WARPING BOARD

barts *pl of* BART

bart·sia \'bärtsēə\ *n* [NL, irreg. fr. Johann *Bartsch* †1738 Ger. physician in Surinam + NL *-ia*] **1** *cap* : a small genus of partly parasitic herbs (family Scrophulariaceae) of the northern hemisphere with opposite leaves and showy irregular flowers in terminal leafy spikes — see ALPINE BARTSIA **2** -s : any plant of the genus *Bartsia*

ba·rukh·zy \bə'rükzē\ *also* **barukhzy hound** *n* -ES *often cap B* [Russ, fr. Peshto *Bārakzī* people of Afghanistan] : AFGHAN HOUND

barunduki *var of* BARONDUKI

barway \'ˌ\ *n* [¹*bar* + *way*] : a gateway closed by bars usu. fitting into posts

bar winding *n* [¹*bar*] : an armature winding consisting of a series of metallic bars connected at their extremities

bar·wing \'ˌ\ *n* [so called fr. the wide white wing stripe] *Austral* : WHITE-EYED DUCK

bar·wise \'ˌwīz\ *also* **bar·ways** \-,wāz\ *adv* [¹*bar* + *-wise* or *-ways*] **1** *heraldry* : in the direction of a bar : HORIZONTALLY **2** *heraldry* : in a line in the direction of a bar — used of two or more charges esp. when not across the middle of the field; compare *in fess* at FESS

barwood \'ˌ\ *n* [¹*bar* + *wood*] : a hard red dyewood of tropical Africa from a tree of the genus *Pterocarpus* but supposed by some to be camwood; *also* : redwood from any of several other African trees

bar-wound \'ˌ\ *adj* : made with bar winding

bary- *comb form* [Gk *bary-*, fr. *barys* — more at GRIEVE] : heavy (*barylite*) (*barysphere*)

bar·y·cen·ter \'barə,sentə(r)\ *n* -s [part trans. of G *baryzentrum*, fr. *bary-* + *zentrum* center] : CENTER OF MASS — **bar·y·cen·tric** \,ˌ'sentrik, -ēk\ *adj*

bar·ye \'barē\ *n* -s [F, fr. Gk *barys* heavy] : ⁷BAR 2

bar·y·lamb·da \,barə'lamdə\ *n, cap* [NL, fr. *bary-* + Gk *lambda*, the letter; fr. the shape of the upper molars] : a genus of large powerful herbivorous mammals (order Pantodonta) from the upper Paleocene of Colorado that have tails like kangaroos and small heads

bar·y·lite \'barə,līt\ *n* -s [ISV *bary-* + *-lite*; orig. formed as G *barylit*] : a mineral $BaBe_2Si_2O_7$ consisting of rare silicate of barium and beryllium occurring in colorless prismatic crystals (hardness 7, sp. gr. 4.03)

ba·ryp·o·da \bə'ripədə\ [NL, fr. *bary-* + *-poda*] *syn of* EMBRITHOPODA

ba·rys·i·lite \bə'risə,līt, ,barə'si,līt\ *n* -s [Sw *barysil* (fr. *bary-* + *silikon* silicon) + E *-ite*] : a rare lead silicate $Pb_3Si_2O_7$ occurring in white cleavable masses

bar·y·sphere \'barə,sfi(ə)r, -iə\ *n* -s [ISV *bary-* + *-sphere*] : the heavy interior portion of the earth within the lithosphere

baryt- *or* **baryto-** *comb form* [ISV, fr. *baryta*] : baryta : barytic (*barytocalcite*)

ba·ry·ta \bə'rīd-ə\ *n* -s [alter. of *barytes* — more at BARITE] : any of several compounds of barium; *esp* : barium monoxide

baryta paper *n* : paper that is coated with a preparation of barium sulfate in gelatin and used after calendering as a support for the light-sensitive emulsion used in photography

baryta water *n* : an aqueous solution of barium hydroxide

baryta white *n* : barium sulfate used as a pigment or extender

baryta yellow *n* : BARIUM YELLOW 2

baryte *or* **barytes** *var of* BARITE

ba·ryt·ic \bə'rid-ik\ *adj* [*baryta* + *-ic*] : of or relating to baryta

bar·y·tine \'barə,tēn\ *n* -s [F, fr. *baryte* barite + *-ine*] : BARITE

ba·ry·to·cal·cite \bə,rīd-ō+\ *n* -s [*baryt-* + *calcite*] : a mineral $BaCa(CO_3)_2$ consisting of white monoclinic barium calcium carbonate (hardness 4, sp. gr. 3.66)

bar·y·ton \'barə,tän\ *n* -s [F — more at BARITONE] **1** : BARITONE 2, 3 **2** [G, fr. It *baritono* — more at BARITONE] : a tenor vox humana organ stop of 16- or 8-foot pitch

[1]**bar·y·tone** \'barə,tōn\ *adj* [Gk *barytonos*, lit., deep-sounding — more at BARITONE] : having an unaccented final syllable — used esp. in Greek grammar

[2]**barytone** \"\ *n* -s : a barytone word (as Greek *philos* "dear" contrasted with *sophos* "wise")

[3]**barytone** *var of* BARITONE

[1]**bas** *pres 3d sing of* BA, *pl of* BA

[2]**bas** \'bəs\ *adv* [Hindi *bas*, fr. Per] *India* : ENOUGH, STOP — often used interjectionally

bas *abbr* basso

ba·sad \'bā,sad\ *adv* [¹*base* + *-ad*] : toward the base (with small bony processes lying ~ to the tree fin rays)

[1]**ba·sal** \'bāsəl *also* -āz-\ *adj* [¹*base* + *-al*] **1** : relating to, situated at, or forming the base; *specif* : ¹RADICAL 1a(2) (~ leaves) **2 a** : of or relating to the foundation, base, or essence : FUNDAMENTAL, BASIC, ESSENTIAL (~ texts in reading) **b** : of, relating to, or essential for maintaining the fundamental vital activities of an organism (as respiration, heartbeat, or excretion) : MINIMAL (~ diet) — see BASAL METABOLISM **3** : serving as or serving to induce an initial comatose or unconscious state that forms a basis for further anesthetization (~ narcosis) (~ anesthetic) — **ba·sal·ly** \-əlē,-əli\ *adv*

[2]**basal** \"\ *n* -s : a basal part or structure; *esp* : a basal plate of an echinoderm

basal age *n* : the mental age level at which all the items on an intelligence test can be creditably passed

basal area *n* : the area of a breast-high cross section of a tree or of all the trees in a stand

basal body *n* **1** : a minute distinctively staining cell organelle found at the base of a flagellum or cilium and resembling a centriole in structure — called also *blepharoplast* **2** : KINETOPLAST

basal cell *n* : one of the innermost cells of the Malpighian layer of the skin

basal-cell carcinoma *n* : a skin cancer derived from and preserving the form of the basal cells of the skin

basal cleavage *n* : cleavage parallel to the base of a crystal or to the plane of the lateral axes

basal complex *n* : FUNDAMENTAL COMPLEX

basal conglomerate *n* : a conglomerate that resting on a surface of erosion and consequently marking an unconformity forms the bottom member of a sedimentary series

basal disk *n* : an expanded basal portion by which certain stalked sessile organisms are attached to the substrate

ba·sa·le \bə'sa(,)lē, -zā-, -ā(,)lē, -ā(,)lē\ *n, pl* **ba·sa·lia** \-lēə\ [NL, fr. E *basal*] : the proximal one of the two or more cartilaginous or bony portions in the axis of any of the paired fins of a fish — compare BASIPTERYGIUM

basal ganglion *n* : any of four deeply placed masses of gray matter within each cerebral hemisphere comprising the caudate nucleus, the lenticular nucleus, the amygdaloid nucleus, and the claustrum — usu. used in pl.

basal granule *n* : BASAL BODY 1

ba·sa·lis \-ləs\ *n, pl* **basa·les** \-,lēz\ [NL, fr. E *basal*] : the basal part of the endometrium that is not shed during menstruation

basal lamina *n* : the part of the gray matter of the embryonic neural tube from which the motor nerve roots arise

basal length *n, anthrop* : distance from gnathion to basion

basal metabolic rate *n* : the rate at which heat is given off by an organism at complete rest usu. determined 12 to 15 hours after ingestion of food and expressed in large calories per square meter of body surface per hour and as a percentage above or below a standard value

basal metabolism *n* : the metabolism of an organism in the fasting and resting state when it uses just enough energy to maintain vital cellular activity, respiration, and circulation as measured by the basal metabolic rate

basal-nerved \¦ˌ¦ˌ\ *adj, of a leaf* : having the veins radiating from the base

basal plane *n* **1** : a plane parallel to the lateral or horizontal axis **2** : a basal pinacoid

basal plate *n* : an underlying structure: as **a** : the ventral portion of the neural tube **b** : the part of the decidua of a placental mammal that is intimately fused with the placenta **c** : the part of a coral corallium immediately below the polyp **d** : any of certain chiefly ventral skeletal plates of an echinoderm

basal ration *n* : a ration furnishing the necessary energy but lacking in one or more accessory food substances (as vitamins) that may be added in varying proportion for the study of their effects

basal rot *n* : a rot affecting the basal parts of a plant; *specif* : a rot of narcissus bulbs due to a fungus (*Fusarium bulbigenum*)

ba·salt \bə'sȯlt, 'bā,sȯlt, 'ba,sȯlt *also* 'bā,zȯlt *sometimes* 'basəlt *or* 'hazalt\ *n* -s [alter. of earlier *basaltes*, fr. L, MS var. of *basanites* touchstone, fr. Gk *basanitēs*, fr. *basanos* touchstone (fr. Egypt *bḫnw*) + *-itēs* -ite] **1** : a dark-gray to black dense to fine-grained igneous rock that is the extrusive equivalent of gabbro, that consists of basic plagioclase, augite, and usu. magnetite with olivine or basalt glass or both sometimes present, that is often vesicular the cavities sometimes being filled with secondary minerals, and that sometimes has a prismatic parting (as in the basalts of the Giant's Causeway, Northern Ireland) and occas. a pillow or ellipsoidal structure **2** *usu* **ba·sal·tes** \bə'sȯl(,)tēz\ : a hard fine-grained black stoneware introduced by Josiah Wedgwood in 1768

basalt dome *n* : a broad rounded dome-shaped volcano formed almost exclusively of basaltic lava — compare SHIELD VOLCANO

basalt glass *n* : a black glassy form of basalt — called also *hyalobasalt*, *vitrobasalt*

ba·sal·tic \bə'sȯltik\ *adj* : relating to, formed of, containing, or resembling basalt (~ lava)

ba·sal·ti·form \bə'sȯltə,fȯrm\ *adj* [*basalt* + *-iform*] : like basalt in form : COLUMNAR

basalt-porphyry *n* : a basalt characterized by prominent phenocrysts of olivine or augite

bas·aluminite \¦bās+\ *n* -s [*basic* + *alumin-* + *-ite*] : a mineral $Al_4(SO_4)(OH)_{10}\cdot5H_2O$ consisting of a basic hydrated aluminum sulfate found in veinlets in siderite at Irchester and Brighton Hill, England, and in France

basal wall *n, bot* : the primary wall in archegoniates that divides the oospore into an anterior and a posterior half

bas·a·nite \'basə,nīt, -azə-\ *n* -s [L *basanites* — more at BASALT] **1** : TOUCHSTONE 1 **2** : an extrusive-igneous rock composed of plagioclase, augite, olivine, and either nepheline or leucite

bas bleu \bäblœ\ *n, pl* **bas bleus** \-œ(z)\ [F *bas-bleu*, fr. *bas* stocking + *bleu* blue] : BLUESTOCKING 1

bas·cart \'ba,skärt\ *n* [blend of *basket* and *cart*] : a waist-high wire basket or pair of baskets on wheels into which shoppers in supermarkets gather their purchases

bas·cine *or* **bas·sine** \ba'sēn\ *adj* [F *bassine*, lit., pan, fr. *bassin* basin, fr. OF *bacin* — more at BASIN] *of a watchcase* : having a flush joint that is barely visible

bascinet *var of* BASINET

bas·col·o·gist \ba'skäləjəst\ *n* -s *usu cap* : a specialist in the Basque language or culture

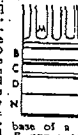
bas·col·o·gy \-əjē\ *n* -ES *usu cap* [*Basco-* (fr. *Basque*) + *-logy*] : the study of the Basque language or culture

bas·cule \'ba,skyül\ *n* -s [F, seesaw, fr. MF, alter. (influenced by *bas* low) of earlier *bacule*, fr. *baculer* to punish by beating the buttocks against the ground, fr. *bas* low + *cul* buttocks — more at BASE, CULET] : an apparatus or structure in which one end is counterbalanced by the other on the principle of the seesaw or by weights (as in a bascule bridge)

bascule bridge *n* : a counterpoised or balanced drawbridge

bascule escapement *n* : the detent escapement in which the detent is pivoted, the tension being supplied by a small hairspring

[1]**base** \'bās\ *n, pl* **bas·es** \'bāsəz\ [ME, fr. MF, fr. L *basis*, fr. Gk, step, stepping, base, pedestal, fr. *bainein* to go, step — more at COME] **1 a** : the bottom of something considered as its support : that on which something rests or stands : FOUNDATION (the ~ of the lamp) (the ~ of the pyramid) (the ~ of the mountain) **b** (1) : the lower part of a wall, pier, or column considered as a separate architectural feature (2) : the lower part of a complete architectural design (as of a monument) **c** : one of the lines or surfaces of a geometrical figure from which an altitude is or is thought to be constructed (the ~ of a triangle) **d** : that part of a bodily organ by which it is attached to another more central structure of the organism (the ~ of the thumb) **e** (1) : the part on, to, or in which the frame and operating parts of a mechanism are fastened (2) : the part (as a panelboard) upon which other parts (as buses, switches, terminal and contact parts) are mounted (3) : the insulated part of a lamp bulb or electron tube through which its intervals make electrical connection with the circuit associated with it **f** : ¹BLOCK 4g **2** : the main ingredient (an exotic drink with a rum ~): as **a** (1) : an essential ingredient of an explosive — compare DOUBLE-BASE POWDER, SINGLE-BASE POWDER (2) : the predominating substance held in solution in a crude petroleum or left as a residue on refining (mixed-*base* crudes) — see ASPHALT-BASE, NAPHTHENE-BASE, PARAFFIN-BASE **b** (1) : an inert supporting or carrying ingredient : an absorbent or adsorbent (as kieselguhr in dynamite) : CARRIER 9 — compare DOPE 3a (2) : an active supporting ingredient (as wood pulp mixed with an oxidizing agent in dynamite) **c** (1) : the usu. inactive ingredient of a preparation serving as the vehicle for the active medicinal principle (the fatty ~ of an ointment) (2) : the chief active ingredient of a preparation — called also *basis* **d** (1) : a transparent support for photographic film (2) : the paper support used for photographic paper **3 a** : the fundamental part of something : basic principle : ESSENCE, FOUNDATION, BASIS, GROUNDWORK (tried to furnish criticism with a psychological ~ —C.I.Glicksberg) (rejuvenating the moral ~ of a society—Herbert Agar) **b** (1) : the fundamental unit or pattern of a rhythm or one of its component parts or the norm of this unit (2) : the nuclear pattern in a complex rhythmic figure or system (3) : BASIS 5 **4** *bases pl, archaic* : a skirt often of velvet or brocade and sometimes of mailed armor that reaches from the waist to the knees **5** : the lower or back part of something without reference to its function as a support: as **a** : the lower part of an heraldic field — usu. used in the phrase *in base*; compare ESCUTCHEON 1 **b** : the lowest part of the hilt of a saber **c** : the pavilion of a cut gem **d** : the underside of a cloud (fly below the cloud ~) **6 a** : the point or line from which a start is made in an action or undertaking (plans to make this city his ~ of operation for six to eight weeks —J.A.Loftus) **b** : a line in a survey which when accurately determined in length and position serves as the origin for computing the distances and relative positions of remote points and objects by triangulation **c** (1) : the locality or the installations on which a military force relies for supplies or from which it initiates operations (a large naval ~) (an advanced ~) (2) : the element on which a military movement or formation is regulated **d** : a number (as 5 in $5^{3.44}$ or 5^7) that is raised to a power; *esp* : the number that when raised to a power equal to the logarithm of a number yields the number itself (the logarithm of 100 to the ~ 10 is 2 since $10^2=100$) **e** : a number equal to the number of units in a given digit's place that for a given system of writing numbers is required to give the numeral 1 in the next higher place (the decimal system uses a ~ of 10); *also* : such a system of writing numbers using an indicated base (convert from ~ 10 to ~ 2) **f** (1) *historical and comparative linguistics* : ROOT, STEM, THEME; *esp* : one reconstructed from words or from the relationships among words in several languages (as assumed Indo-European *bher-* "to carry" reconstructed from Greek *pherein*, Latin *ferre*, Old English *beran*, and their cognates) (2) *descriptive linguistics* : the word or morpheme, which may be a bound form but not an affix, selected as a convenient point of departure in the analysis of complex words or derivatives (as *play* used in the analysis of *played* and *playful*, *sing* used in the analysis of *sings*, *sang*, *sung*, and *song*, or *acet-* used in the analysis of *acetal* and *acetate*) **g** : the basal pinacoid of a crystal **h** : the quantity equaling 100 from which variations in an index number are measured (the 1946–49 profit ~) **7 a** : the starting place or goal in various games **b** *obs* : PRISONER'S BASE **c** : any one of the four stations at the corners of a baseball infield (was thrown out at first ~) **8 a** : a compound (as lime, ammonia, a caustic alkali, or an alkaloid) capable of reacting with an acid to form a salt either with or without the elimination of water, its aqueous solutions if it is water-soluble having an acrid brackish taste and turning litmus blue : a compound (MOH) containing the hydroxide ion (OH^-) or hydroxyl group (OH) that is capable of yielding in aqueous solution a hydroxyl ion together with the cation (M^+), the degree of ionization in dilute solutions of strong bases (as sodium hydroxide, calcium hydroxide, and choline) being virtually complete and that of weak bases (as ammonium hydroxide and many organic bases) being in the neighborhood of one percent or less **b** *according to the Brønsted-Lowry system* : a molecule (as ammonia) or ion (as hydroxyl or nitrate) that can take up a proton from an acid : a proton acceptor (the chloride ion is the conjugate ~ of hydrogen chloride) **c** *according to the G.N.Lewis system* : a compound (as ammonia, ether, or benzene) or a negative ion (as hydroxyl) capable of giving up to an acid an unshared pair of electrons which then form a covalent chemical bond — called also *Lewis base* **9** : the least number of natural cards that will form a canasta when a required number of natural or wild cards is added — **off base 1** : completely or absurdly mistaken (any man who said such a thing is certainly *off base*) **2** : by surprise : UNAWARES (the sudden question caught him *off base*)



base of a column: *B* upper torus; *C* scotia; *D* lower torus; *F, F, F,* fillets; *M* shaft; *N* plinth

[2]**base** \"\ *vb* -ED/-ING/-S *vt* **1 a** : to make or form a foundation for (great roots *based* the tree columns —George Macdonald) **b** : to serve as a base for (these carriers can ~ 100 planes) **c** : to establish or maintain a base for (would be necessary to ~ them at specially designated . . . strategic points —Vera M. Dean) **2** : to use as a base or basis for : ESTABLISH, FOUND — used with *on* or *upon* (~*s* his position on a wide and shrewd scrutiny of man —A.L.Locke) (*basing* her life-sized portrait . . . on contemporary evidence —Harry Levin) ~ *vi* **1** : to become based — used with *on* or *upon* (the value of diamonds ~*s* on the gem value —G.S.Brady) **2** : to establish or main-

[redacted]

[redacted]

tain one's base ⟨would fly on to Luzon after the attack and ~ there overnight —Fletcher Pratt⟩

syn BASE, FOUND, GROUND, BOTTOM, STAY, and REST can mean, in common, to provide with or serve as a basis. BASE now usu. applies to what underlies a belief, a system of thought, a judgment, a hope, and so on ⟨a conviction not *based* on any ascertainable fact⟩ ⟨a tax *based* on prospective earnings⟩ ⟨a religion *based* on faith as much as principle⟩ FOUND is very close to BASE but usu. adds the idea of something consciously advanced as support (of an opinion, a judgment, and so on) ⟨an opinion *founded* on a careful written analysis of facts⟩ ⟨this criticism is *founded* in misconception —B.N.Cardozo⟩ ⟨the terrible old mythic story on which the drama was *founded* —Matthew Arnold⟩ GROUND implies or connotes an implanting (as in the ground) to give solidity and firmness ⟨a love *grounded* in understanding and trust⟩ ⟨*grounded* all his work as a novelist on the faithful study of human nature —M.P.Linehan⟩ ⟨America was *grounded* not in the overthrow of the feudal past but in escape from it —Richard Hofstadter⟩ BOTTOM, rarer in this sense than the other terms, implies a broad and strong base ⟨his report was *bottomed* on sober statistics —*Time*⟩ ⟨*bottomed* on ideas to which everyone subscribes today —C.G.Bowers⟩ STAY implies a support that keeps upright or prevents from falling ⟨*stay* a tipping barn with heavy supporting timbers on one side⟩ ⟨his nature looked coldly upon its early faith and sought to *stay* itself with rational knowledge —H.O.Taylor⟩ REST stresses reliance upon something as a base or fundamental support, usu. figurative ⟨continuing progress based on science and technology . . . the foundation upon which our prosperity and our increasing standard of living *rest* —H.H.Curtice⟩ ⟨their academic reputations *rest*, quite largely, upon their academic power —C.W.Mills⟩ ⟨the cultures of the ancient empires of the Near East, of Greece and Rome, and of medieval Europe, all *rest* on the technical achievements of the Neolithic Age —Benjamin Farrington⟩

3**base** \"\ *adj* [1*base*] **1** : constituting or serving as a base ⟨are now setting up a string of ~ camps —*Time*⟩ **2** : BASIC ⟨the right to work is a ~ right —Ira Mosher⟩

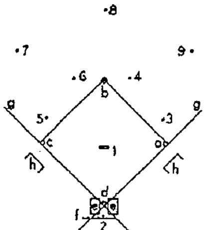
4**base** \"\ *adj* -ER/-EST [ME *bas*, fr. MF, fr. ML *bassus* fat, short, low] **1** *archaic* : of little height : not high or tall ⟨the cedar stoops not to the ~ shrub's foot —Shak.⟩ **2** *obs* : low in place or position ⟨fall to the ~ earth from the firmament —Shak.⟩ **3** *obs* : 3BASS **4** *archaic* **a** : of humble birth or position : LOWLY, PLEBEIAN, POOR ⟨~ in kind and born to be a slave —William Cowper⟩ **b** : of illegitimate birth : BASTARD ⟨Edmund the ~ shall top the legitimate —Shak.⟩ **5 a** : like a villein : SERVILE ⟨a ~ tenant⟩ **b** : held by villenage ⟨~ tenure⟩ **6** : of inferior quality : SHABBY, COARSE, DEBASED: as **a** (1) : alloyed with inferior metal ⟨~ gold⟩ (2) : made of inferior metal ⟨~ coins of aluminum⟩ **b** *of language* : not classical ⟨~ Latin⟩ **7** : having no dignity of sentiment or trustworthiness : LOW-MINDED, MEANSPIRITED, SHAMEFUL, IGNOBLE, UNWORTHY ⟨seemed a ~ betrayal of idealism —L.M.Sears⟩ **8** : lacking higher values : DEGRADING, MENIAL ⟨citizens go on existing with a ~ mechanical kind of life like that of insects —Stephen Spender⟩ **9** : of comparatively little value : not precious — compare BASE METAL

syn LOW, VILE: BASE stresses the ignoble; it may suggest cruelty, treachery, greed, or grossness ⟨all those features which distinguish the errors of magnanimous and intrepid spirits from *base* and malignant crimes —T.B.Macaulay⟩ ⟨*base* self-centered indulgence and selfish ambition —W.R.Inge⟩ LOW may connote crafty cunning, vulgarity, or immorality ⟨a man who by exercising a *low* sort of cunning, has managed to grab three or four millions of money selling bad whiskey —G.B. Shaw⟩ ⟨some sporting events of a *low* type, such as setting on men, women, or animals to fight —G.M.Trevelyan⟩ VILE, the most extreme of these three words, often suggests depravity or filth ⟨a jeering intention in his meanly unctuous tone, something more *vile* than mere cruelty —Joseph Conrad⟩ ⟨*vile* abuse and unbelievable blasphemies poured from her snarling lips —W.H.Wright⟩ ⟨the jail was a *vile* place, in which most kinds of debauchery and villainy were practiced, and where dire diseases were bred —Charles Dickens⟩ or, unlike BASE and LOW, is often used as a strong synonym for *objectionable* or *poor* ⟨curses . . . for the *vile* drinks he had been the means of introducing there —W.M.Thackeray⟩

5**base** [4*base*] *obs var of* 2BASS

base angle *n* [1*base*] : the horizontal angle between the base line and the orienting line in artillery fire measured from the base line in the same direction as angles are measured by the sight on the gun

base·ball \'⸗,⸗\ *n, often attrib* [1*base* (goal) + *ball*] **1** : a game played with a ball, bat, and gloves between 2 teams of 9 players each on a large field centering upon 4 bases that form the corners of a square 90 feet on each side, each team having a turn at bat and in the field during each of the 9 innings that constitute a normal game, the winner being the team that scores the most runs — see BALL 3a, b, STRIKE, OUT; FAIR BALL, FOUL BALL; INFIELD, OUTFIELD **2** : a ball having a cork or rubber center wound tightly with twine and covered with two pieces of bleached white horsehide stitched together, officially from 5 to 5¼ ounces in weight and from 9 to 9¼ inches in circumference **3** : a form of seven-card stud poker in which nines and threes are wild and threes and fours when dealt face up give the recipient certain special privileges



baseball field: *1* pitcher, *2* catcher, *3* first baseman, *4* second baseman, *5* third baseman, *6* shortstop, *7* left fielder, *8* center fielder, *9* right fielder, *a* first base, *b* second base, *c* third base, *d* home plate, *e* batter's box, *f* catcher's line, *g* foul line, *h* coach's box

baseball stitch *n* : a stitch for making two edges just meet worked under and over from the inside outward and used esp. in seaming baseball covers and mending tears in sails

baseboard \'⸗,⸗\ *n* [1*base* + *board*] : a board situated at or forming the base of something ⟨the ~ of a camera⟩; *specif* : a protecting or finish molding of board or other material covering the joint of a wall and the adjoining floor

baseboard heating *n* : panel heating by means of baseboards

baseborn \'⸗'⸗\ *adj* [4*base* + *born*] **1 a** : of humble birth : LOWLY **b** : of illegitimate birth : BASTARD **2** : MEANSPIRITED, IGNOBLE

base box *n* : a unit of area for tin plate and terneplate equal to 31,360 square inches or 217.78 square feet or 20.232 square meters corresponding to the area covered by 112 plates of 14 by 20 inches each

base broom *n* : WOODWAXEN

base bullion *n* [4*base*] : crude lead containing silver or gold and silver

base burner *n* [1*base*] : a stove in which the fuel is fed from a hopper as the lower layer is consumed

base circle *n* [1*base*] : the circle of an involute gear wheel from which the involute forming the outline of the tooth face is generated

base coat *n* [3*base*] **1** : the plaster underlying the finish coat and consisting of a single coat or of separately applied scratch coat and brown coat **2** : PRIMING 1b(2)

base course *n* [3*base*] **1 a** : the first or lowest course of a wall (as of a foundation wall or of the wall of a building above the basement) **b** : the bottom layer of material laid down in the construction of a pavement **2** *of a ship* : a straight-line course ⟨the destroyer turned back to *base course*⟩

base-court \'⸗,⸗\ *n* [MF *basse-court*, fr. *basse* (fem. of *bas* low) + *court* — more at *base*] **1 a** : the lower or outer court of a castle or mansion : BAILEY **b** : the rear courtyard of a farmhouse **2** : an English inferior court of law

based \'bāst\ *adj* [1*base* + *-ed*] : having a base or having as a base ⟨firmly ~ ice⟩ ⟨a soundly ~ argument⟩

ba·se·dow's disease \'bäzə,dōz-\ *n, usu cap B* [after Karl von *Basedow* †1854 Ger. physician] : EXOPHTHALMIC GOITER

base elbow *n* [1*base*] : a cast-iron pipe bend having a flange or pad cast on it as a seat for a supporting column or bracket

base esquire *n* [4*base*] *heraldry* : the lower of the halves of a canton divided diagonally

base exchange *n* [1*base*] : CATION EXCHANGE

base fee *or* **base fee simple** *n* [3*base*] **1** : a determinable fee; *broadly* : a defeasible fee-simple estate (as a conditional fee) **2** *obs* **a** : an estate held by a tenant at the will of his lord or superior **b** : the status of an estate conveyed by a tenant in tail out of possession as a fee simple without proper adherence to the relevant rules of law

basehearted \'⸗¦⸗\ *adj* : having a base heart

base hit *n* [1*base*] : a hit in baseball that enables the batter to reach base safely with no error being made and no base runner being forced out on the play

base horehound *n* [4*base*] **1** : WHITE DEAD NETTLE **2** : a common European woundwort (*Stachys germanica*) with ashy gray foliage and pinkish white flowers

base knob *n* [1*base*] : a knob often made partly of rubber and fastened to a baseboard to prevent a door from striking the wall

ba·sel \'bäzəl, 'baz-\ *adj, usu cap* [fr. *Basel*, Switzerland] : of or from the city of Basel, Switzerland : of the kind or style prevalent in Basel

base·less \'bāsləs\ *adj* [1*base* + *-less*] : having no base : GROUNDLESS ⟨a ~ fear⟩ — **base·less·ly** *adv* — **base·less·ness** *n* -ES

1**baselevel** \'⸗¦⸗⸗\ *n* [1*base* + *level*] : the level below which a land surface cannot be reduced by running water

2**baselevel** \"\ *vt* : to reduce to or toward the condition of a plain at baselevel

baselevel plain \'⸗,⸗⸗-\ *n* : a plain produced by the degradation of a region to its baselevel — compare PENEPLAIN

base line *n* [1*base*] : a main line taken as or representing a base: as **a** : BASE 6b; *specif* : a line extending east and west from a chosen reference point on a principal meridian and forming with the meridian a pair of coordinate axes for locating township and section corners — used in U.S. public-land surveying **b** : the line joining the base piece and the base point in artillery fire **c** : the lowest horizontal line in a profile drawing of a ship used as a base for vertical measurements **d** *of a perspective drawing* : the line formed by the intersection of the ground plane and the picture plane **e** : the area within which a baseball player must keep when running between bases **f** : the back line at each end of a tennis court — see TENNIS illustration **g** : the lower horizontal guideline for aligning capitals in freehand lettering **h** : a known quantity used as a control for further experimentation

base·lin·er \'bā¦slīnə(r)\ *n* -S [*base line* + *-er*] : a tennis player who usu. plays near the base line

ba·sel·la \bə'selə, -'ze-\ *n, cap* [NL, prob. fr. a native name in India] : a genus of herbaceous annual or biennial vines (the type of the family Basellaceae) having sessile flowers on thickened pedicels and being natives of tropical Asia and Africa where they are used as potherbs — see MALABAR NIGHTSHADE

bas·el·la·ce·ae \,basə'lāsē,ē, -azə-\ *n pl, cap* [NL, fr. *Basella*, type genus + *-aceae*] : a small family of usu. climbing herbs (order Caryophyllales) sometimes included in the Chenopodiaceae but distinguished by having the calyx and corolla dissimilar — **bas·el·la·ceous** \¦⸗⸗¦⸗shəs\ *adj*

base·ly *adv* [4*base* + *-ly*] : in a base manner : DISHONORABLY, IGNOBLY, SHAMEFULLY ⟨few . . . have been clearly and ~ faithless to their society —C.W.deKiewiet⟩

base·man \'bāsmən\ *n, pl* **basemen** : a man stationed at a base

base map *n* [3*base*] : a map having only essential outlines and used for the plotting or presentation of specialized data of various kinds

base·ment \'bāsmənt\ *n* -S *often attrib* [prob. fr. 1*base* + *-ment*] **1** : the architectural member that serves as a pedestal or substructure for the main order; *specif* : the ground floor facade in Renaissance architecture **2 a** : the part of a building that is wholly or partly below ground level; *esp* : such a room having overlaid or hard-surface flooring and housing a furnace — compare CELLAR **b** : the interior at ground level in a basement house or in a building having a basement facade **3** : the lowest or fundamental part of anything ⟨the ~ of the fountain —Charles Dickens⟩ **4 a** : BASEMENT COMPLEX **b** : a compact firm rock underlying less firmly consolidated earth materials ⟨atolls can grow on various types of ~s —F.P.Shepard⟩ **5** *chiefly New Eng* : an indoor school toilet or washroom ⟨the boy's ~⟩

B basement

basement complex *n* **1** : the assemblage of metamorphic and igneous rocks underlying stratified rocks in a particular region **2** : the Archean rocks — compare FUNDAMENTAL COMPLEX

basement house *n* : a dwelling in which the principal drawing rooms are located at least one story above ground level with the main entrance at ground level or one story above and reached by exterior steps

basement membrane *n* : a delicate connective tissue membrane commonly composed of a single layer of flat cells and underlying the epithelial cells of many organs

base metal *n* [4*base*] **1** : a metal or alloy (as zinc, lead, or brass) of comparatively low value and relatively inferior in certain properties (as resistance to corrosion) — opposed to *noble metal* **2** : the metal to which a coating or plating is applied : the metal existing underneath a coating or plating **3** : the chief constituent of any alloy **4** : the metal composing parts to be welded

base molding *n* [1*base*] : a molding along the upper margin of a baseboard or other plinth

bas·en·dite \'bā'sen,dīt\ *n* -S [1*base* + *endite*] : either of a pair of lobes attached at the end of each of the specialized paired appendages of a crustacean — compare ENDITE, EXITE

base·ness \'bāsnəs\ *n* -ES [4*base* + *-ness*] **1** : the quality or state of being base ⟨moral ~⟩ **2** : a base act or trait ⟨perpetrate a ~ so unmixed —Robert Browning⟩

base net *n* [1*base*] : a system of triangles and quadrilaterals including and immediately adjacent to a base line in a triangulation system

ba·sen·ji \bə'senjē\ *n* [of Bantu origin; akin to Lingala & Tshiluba *basenji*, pl. of Lingala *mosenji*, Tshiluba *musenji* native, inhabitant of the hinterland] **1** *usu cap* : an African breed of small compact curly-tailed chestnut-brown dogs that rarely bark **2** -S *sometimes cap* : any dog of the Basenji breed

base of fire [1*base*] : an element of or one or more military units that give supporting fire to an attacking unit

base on balls [1*base*] : an advance to first base given to a baseball player who during his time at bat receives four pitches outside the strike zone ⟨was given an intentional *base on balls* in the seventh inning⟩ — called also *pass*, *walk*

base paper *or* **base stock** *n* [1*base*] : BODY PAPER

base path *n* [1*base*] : the area between the bases of a baseball field used by a base runner

base pay *or* **base salary** *or* **base wage** *n* [1*base*] : BASIC WAGE; *specif* : the minimum pay for a given rank or grade of a member of the armed forces ⟨retired for life upon three-quarters of his *base pay* —Nancy B. Shea⟩

base period *n* [3*base*] : a period of business or economic activity used as a basis or reference point esp. for indexing, calculating, estimating, or adjudicating prices, taxes, compensation, income, and production

base piece *n* [1*base*] : the piece of a gun battery for which the initial firing data are computed

baseplate \'⸗,⸗\ *n* [1*base* + *plate*] **1** : a plate that serves as a base or support: as **a** : the foundation plate of heavy machinery (as of a steam engine) : BEDPLATE **b** : the steel or cast-iron plate on which a column rests **c** : the metal plate that serves as a base and firing support for the breech end of a mortar **2 a** : the portion of an artificial denture in contact with the jaw **b** : the sheet of plastic material used in the making of trial denture plates

baseplug \'⸗,⸗\ *n* [1*base* + *plug*] : an electric wall receptacle; *esp* : one in or near the baseboard

base price *n* [3*base*] **1** : a price for a standard commodity from which variations are readily computed (as by a formula) **2** : a price before discounts and extras

baser *comparative of* BASE

base rate *n* [3*base*] : an established and usu. guaranteed rate of pay per unit of time (as per hour or day) or for production at the standard rate

base right *n* [3*base*] : the right in Scots law acquired by a disponee taking feudal property to hold as subvassal

base ring *n* [1*base*] **1** : a projecting band of metal around the breech of a muzzle-loading cannon — see CANNON illustration **2** : the circular base of a heavy gun carriage

base rocker *or* **base rocking chair** *n* [1*base*] : a rocking chair fastened upon a base that is usu. mounted on casters

base runner *n* [1*base*] : a baseball player of the team at bat who is on base or is attempting to reach a base — **base·running** \'⸗,⸗⸗\ *n*

bases *pl of* BASE *or of* BASIS, *pres 3d sing of* BASE

base shoe *n* [1*base*] : a narrow molding often of quarter round joining the bottom of a baseboard and the floor

basest *superlative of* BASE

base stock method *n* [3*base*] : an accounting method of valuing inventories by carrying on the books a minimum quantity of a commodity at the same low fixed price from year to year and valuing the quantity in excess of the minimum at a separate price which is usu. the lower of cost or market value — compare LAST IN, FIRST OUT

base stone *n* [3*base*] : FOOTING STONE

base surge *n* [1*base*] : the cloud of mist, water, and debris that spreads outward from the surface point of an underwater atomic explosion

base time *n* [3*base*] : the time calculated as the normal time required by a qualified individual working at normal pace for completion of a given work cycle with no allowance for delay or fatigue and personal needs

1**bash** \'bash, -aa(ə)-, -ai-\ *vb* -ED/-ING/-ES [origin unknown] *vt* : to strike violently : BEAT, KNOCK ⟨~ him on the head with a club⟩ : smash by a blow — often used with *in* ⟨the tree ~*ed* in the roof⟩ ~ *vi* **1** : CRASH ⟨the car ~*ed* into a tree⟩ **2** *Brit* : HIT, KNOCK ⟨a branch ~*ing* against the house⟩; *also* : to punch with the fist — **bash one's ear** *chiefly Austral* : to talk long and insistently to one

2**bash** \"\ *n* -ES **1** *chiefly Brit* : a forceful blow **2** *slang Brit* : a good time : ENTERTAINMENT

ba·sha \bä'shä, '⸗(,)⸗\ *n* -S [Assamese] : an Assamese hut typically made of bamboo and grass

bash·am's mixture \'bashəmz-\ *n, usu cap B* [after William R. *Basham* †1877 Eng. physician] : an aromatic solution of iron and ammonium acetate formerly used as a hematinic

bashaw *often cap, var of* PASHA

bash·er \'bashə(r), -aash-, -aish-\ *n* -S [1*bash* + *-er*] : one that bashes; *esp, chiefly Austral* : a criminal who beats and robs his victims

bash·ful \'bashfəl, -aash-, -aish-\ *adj* [obs. *bash* to be abashed (fr. ME *basshen*, short for *abaisshen*) + *-ful* — more at ABASH] **1** : inclined to shrink from public attention : socially shy or timid : SELF-CONSCIOUS, DIFFIDENT ⟨he hesitated, awkward and ~, shifted his weight from one leg to the other —Jack London⟩ ⟨they considered themselves a tough outfit and weren't ~ about letting anybody know it —F.B. Gipson⟩ **2** : characterized by, showing, or resulting from extreme sensitiveness, self-consciousness, or shyness ⟨found that ~ words tumbling from his tongue's end really spelled themselves out into sensible talk —Carl Sandburg⟩ **syn** see SHY

bashful billy *n, usu cap 2d B* : LORIS 1b

bash·ful·ly \-fəlē, -li\ *adv* : in a bashful manner

bash·ful·ness \-fəlnəs\ *n* -ES : the quality or state of being bashful

ba·shi-ba·zouk \,bashēbə'zük\ *n* -S [Turk *başı bozuk* irregular soldier, fr. *baş* head, leader + *bozuk* depraved, corrupt] **1 a** : a member of an irregular ill-disciplined auxiliary of the Ottoman Empire **b** : IRREGULAR **2** : a turbulent ill-disciplined person

bashing *n* -S [fr. gerund of 1*bash*] : BEATING ⟨they have both had a ~⟩

bash·kir \(')bash¦ki(ə)r\ *n, pl* **bashkir** *or* **bashkirs** *usu cap* [Russ, of Turkic origin; akin to Jagatai *bašǧyr* Bashkir, Chuvash *pušḱart*] **1 a** : a Turkic-speaking Muslim people between the Volga and the Ural mountains regarded as tatarized Finns **b** : a member of the Bashkir people **2** : the language of the Bashkirs

bash·lyk *also* **bash·lik** \(')bash¦lik\ *n* -S [Russ *bashlyk*, fr. Turk *başlık* hood, fr. *baş* head] : a protective hood with long ends for use as a scarf worn esp. by the Russian military

ba·si \'bäsē\ *n* -S [native name in the Philippines] : a fermented beverage prepared by natives of the Philippines

basi- \in pronunciations below ¦⸗⸗ = ¦bāsē (bef vowels or consonants) or -sə (bef consonants)\ *also* **baso-** *comb form* [ISV, fr. L *basis*] **1 a** : base : lower part ⟨*basi*petal⟩ **b** : at or near the base ⟨*basi*fixed⟩ ⟨*basi*glandular⟩ **c** : of or belonging to the base of ⟨*basi*cranial⟩ **2 a** : chemical base ⟨*basi*fy⟩ **b** : subsilicic and ⟨*basi*ophitic⟩

ba·si·al \'bāsēəl\ *adj* [*basi-* + *-al*] : of or relating to the basion

1**ba·si·branchial** \¦⸗⸗ *at* BASI- + \ *adj* [*basi-* + *branchial*] : of, relating to, or being a median bone or cartilage at the ventral point of a branchial arch

2**basibranchial** \"\ *n* -S : a basibranchial bone or cartilage

ba·si-bregmatic height \¦⸗⸗+ . . . -\ *var of* BASION-BREGMA HEIGHT

1**ba·sic** \'bāsik, ¦ēk *sometimes* -āz|\ *adj* [1*base* + *-ic*] **1** : of, relating to, or forming the base or essence : FUNDAMENTAL, ESSENTIAL, IRREDUCIBLE ⟨a ~ fact⟩ ⟨a ~ argument⟩ ⟨~ truths⟩ **2** : constituting or serving as the basis or starting point ⟨a ~ house⟩ **3 a** : of, relating to, or characteristic of a base ⟨~ groups⟩ ⟨~ nitrogen⟩ — compare ALKALINE **b** : having an alkaline reaction ⟨~ compounds⟩ ⟨a ~ catalyst⟩ **c** *of salts* : derived by partial neutralization ⟨~ lead carbonate⟩ ⟨~ bismuth chloride⟩ **d** : containing or involving the use of alkaline material ⟨a furnace with a ~ lining⟩ — see BASIC PROCESS **e** : base-forming ⟨lime is a ~ oxide⟩ **4** *of rocks* : containing relatively little silica : SUBSILICIC — opposed to *acid* **5** : relating to or made by a basic process ⟨~ steel⟩ ⟨~ rails⟩ **6** *of language* : having a vocabulary that consists of a very small number of words but that can be used to convey a wide range of ideas or information ⟨~ French⟩ **7** : assigned for general duties within a military organization ⟨a ~ private⟩ **8** : prescribed and nominal — used of standards (as of size) that are the basis for the calculation of allowances and tolerances

2**basic** \"\ *n* -S **1** : something that is basic : FUNDAMENTAL — usu. used in pl. ⟨the ~*s* of honesty⟩ ⟨the ~*s* of sewing⟩ **2** : BASIC TRAINING ⟨took his ~ at Keesler Field⟩

basic airman *n* : an airman undergoing basic training in the U.S. Air Force

ba·si·cal·ly \|ək(ə)lē, |ēk-, -li\ *adv* : FUNDAMENTALLY, ESSENTIALLY

basic anxiety *n, psychol* : a feeling of helplessness and personal isolation

basic crew *n* **1** : the group or number of employees considered necessary for continuous operation (as of a business or factory) **2** : a limited number or prescribed group of employees subject to guaranteed wage provisions in a labor contract

basic crop *or* **basic commodity** *n* : an agricultural product deemed of sufficient economic or political importance to be designated by the U.S. Congress for special production controls or price supports

basic dress *n* : a simple classic dress usu. of a solid color and adaptable to many occasions by a change of accessories

basic dye *or* **basic color** *n* : any of various chiefly synthetic dyes reacting as bases because of the presence of certain nitrogen-containing groups (as amino groups), producing clear

Webster's Third New International Dictionary

OF THE ENGLISH LANGUAGE

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SPRINGFIELD, MASSACHUSETTS, U.S.A.

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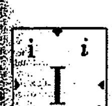
Library of Congress Cataloging in Publication Data
Main entry under title:

Webster's third new international dictionary of the English language, unabridged: a Merriam-Webster/editor in chief, Philip Babcock Gove and the Merriam-Webster editorial staff.
p. cm.
ISBN 0-87779-201-1

1. English language—Dictionaries. I. Gove, Philip Babcock, 1902–1972. II. Merriam-Webster, Inc.
PE1625.W36 1993
423–dc20 93-10630
CIP

MADE IN THE UNITED STATES OF AMERICA
484950QPH9796

[redacted]



¹i \ˈī\ *n, pl* i's *or* is \ˈīz\ *often cap, often attrib* **1 a :** the ninth letter of the English alphabet **b :** an instance of this letter printed, written, or otherwise represented **c :** a speech counterpart of orthographic *i* (as long *i* in *side*, short *i* in *sit*, or *i* in French *élite*) **2 :** ONE — see NUMBER table **3 :** a printer's type, a stamp, or some other instrument for reproducing the letter *i* **4 :** someone or something arbitrarily or conveniently designated *i* esp. as the ninth in order or class **5 :** something having the shape of the capital letter I **6 :** a unit vector parallel to the x-axis **7** [abbr. for *incomplete*] **a :** a grade assigned by a teacher or examiner rating a student's work as incomplete **b :** one graded or rated with an I

²I \(ˌ)ī, ə, *often* ä *or* ä *when unemphatic esp in contracted forms as "I'm" & "I'll"*\ *pron, cap* [ME *ich, I,* fr. OE *ic;* akin to OHG *ih* I, ON *ek,* Goth *ik,* L *ego,* Gk *egō, egōn,* Skt *aham*] **1 :** the one who is speaking or writing ⟨*I* shall not want —Ps 23:1 (AV)⟩ — used as a nominative pronoun of the first person singular by one speaking or writing to refer to himself as the doer of an action ⟨*I* will not hurt you⟩ ⟨whither thou goest, *I* will go —Ruth 1:16 (AV)⟩ or the subject of a predicated condition ⟨*I* don't feel very well today⟩ or sometimes in the predicate after forms of *be* ⟨it will not be *I* —D.D.Eisenhower⟩ ⟨it is *I* —Mk 6:50 (AV)⟩ or in comparisons after *than* or *as* when the first term in the comparison is the subject of a verb ⟨you can do it just as well as *I*⟩ ⟨he writes much better than *I*⟩ ⟨thou art stronger than *I* —Jer 20:7 (AV)⟩ or in some absolute or elliptical constructions esp. when not used with a prepositional phrase or an adjective or a participle ⟨who, *I*? You're foolish to say that anyone would do it⟩ or after *but* in a compound subject ⟨no one but *I* could have known —H.G.Wells⟩ — see ME, MINE, MY; compare WE **2 a** *now chiefly substand* **:** ME — used in a compound object ⟨belongs to my mother and *I*⟩ ⟨between you and *I*⟩ ⟨he saw my brother and *I*⟩ **b** *now dial Eng* **:** ME — used emphatically as object of a verb ⟨give poor *I* another chance⟩ or preposition ⟨give the ball to *I*⟩ ⟨my father hath no child but *I* —Shak.⟩ **3 :** the one who acts as authorized spokesman of a social or military system (as an army) ⟨*I* order you to report for duty⟩

³I \ˈī\ *n, pl* I's *or* Is *cap* **1 :** someone possessing and aware of possessing a distinct and personal individuality **:** SELF, EGO ⟨there is but one *I* —Mary B. Eddy⟩ ⟨society has been atomized down to its elemental particles each of which is an *I* —W.P. Webb⟩; *also* **:** the quality or state of possessing such individuality ⟨the crowd is like a community in that it can be any size, the difference being that the We precedes the *I* —Howard Griffin⟩ **2 :** an excessively egotistic person **;** one that uses the first person pronoun excessively ⟨just a big *I*⟩ **3 :** a dichotomous part of one's self ⟨the other *I*⟩

⁴i *or* i' \ı\ *now chiefly dial var of* IN

⁵I *abbr var of* AYE

⁶I *abbr, often cap* **1** [L *id*] that **2** [L *imperator; imperatrix*] emperor; empress **3** imperial **4** incendiary **5** incomplete **6** independent **7** indicated; indicative **8** industrial **9** infantry **10** infield **11** inhibitory **12** initial **13** inner **14** inside **15** inspector **16** instantaneous **17** institute; institution **18** instrumental **19** intelligence **20** interceptor **21** interest **22** international **23** interstate **24** intransitive **25** Iraqi **26** iron **27** island; isle **28** Israeli

⁷I *symbol, cap* **1** iodine **2** candlepower **3** electric current **4** moment of inertia **5** imaginary unit

i- *comb form* [inactive] **:** inactive (sense c) ⟨*i*-inositol⟩ — usu. joined to second element with a hyphen

i- *comb form* [by shortening] **:** IS- 2b ⟨*i*-butyl⟩ — usu. joined to second element with a hyphen

-i- [ME, fr. OF, fr. L, thematic vowel of most nouns and adjectives in combination] — used as a connective vowel to join two elements of usu. Latin origin, being either identical with (*auriform*) or representative of (*Herbivora*) an original Latin stem vowel or simply inserted (*cantilever*); compare -O-

¹-ia \ēə, yə, ēə\ *n suffix* [NL, fr. L & Gk, suffix forming feminine abstract nouns] **1** -s **:** pathological condition ⟨pneumon*ia*⟩ ⟨hyster*ia*⟩ ⟨diphther*ia*⟩ **2 :** genus of plants or animals ⟨Wistar*ia*⟩ ⟨Osm*ia*⟩

²-ia \"\ *n pl suffix* [NL, fr. L (neut. pl. of -*ius,* adj. ending) & Gk neut. pl. of -*ios,* adj. ending] **1 :** taxonomic division (as class, order) of plants or animals ⟨Cryptogam*ia*⟩ ⟨Mammal*ia*⟩ **2 :** things belonging to or derived from or relating to (something specified) ⟨Marylandi*a*⟩ ⟨tabloid*ia*⟩

³-ia *pl of* -IUM

IA *abbr* **1** incorporated accountant **2** infected area **3** *often not cap* [L *inter alia*] among other things **4** international angstrom

IAA *abbr* indoleacetic acid

IAC *abbr* **1** industry advisory committee **2** interview-after-combat

-ial \ēəl, yəl, ēəl, əl\ *adj suffix* [ME, fr. MF -*iel,* -*ial,* fr. L -*ialis,* fr. -*i-* + -*alis* -al] **:** ¹-AL ⟨manor*ial*⟩

iamb \ˈīˌam, -ˌa(ə)m *also* -mb\ *n, pl* iambs \-mz\ [L *iambus,* fr. Gk *iambos*] **1 :** a metrical foot of two syllables unstressed and stressed respectively (as in *above, invent,* and Tennyson's 4-foot line "he watches from his mountain walls") or short and long respectively (as in classical prosody) **:** a disyllabic rising cadence — symbol ⏑ –; compare TROCHEE **2 :** verses written in iambs

iam·bel·e·gus \ˌīˌamˈbeləgəs\ *n* -ES [LL, fr. Gk *iambelegos,* fr. *iambos* + *elegos* song of mourning or lamentation, prob. of non-IE origin] **:** a verse used in classical prosody consisting of an iambic dimeter and half an elegiac pentameter

¹iam·bic \īˈambik, -bēk\ *n* -S [L *iambicus,* adj.] **1 :** IAMB **2 :** a piece of usu. satiric verse written in iambs (as that developed by the Ionian Greeks in the period succeeding the epic) **:** a lampoon written in iambs

²iambic \(ˈ)=ˌ==\ *adj* [L *iambicus,* fr. Gk *iambikos,* fr. *iambos* + -*ikos* -ic] **:** relating to or consisting of iambs or iambics ⟨~ verse⟩ — iam·bi·cal·ly \-bək(ə)lē, -bēk-, -li\ *adv*

iam·bist \=ˈ=bəst, ˈ=ˌ=-\ *n* -S [Gk *iambistēs,* fr. *iambizein* to write iambs, fr. *iambos* + -*izein* -ize] **:** one who writes iambic verse

iam·bog·ra·pher \ˌīˌamˈbägrəfə(r)\ *n* -S [MGk *iambographos* writer of iambs (fr. Gk *iambos* + -*graphos,* fr. *graphein* to write) + E -*er* — more at CARVE] **:** IAMBIST; *esp* **:** one given to or noted for writing iambic lampoons

iam·bus \īˈambəs\ *n, pl* iambus·es \-bəsəz\ *also* iam·bi \-ˌbī\ [L, fr. Gk *iambos*] **:** IAMB

-ian \ēən, yən, ēən, ən\ — see -AN

-iana — see -ANA

I and E *abbr* information and education

I and P *abbr* indexed and paged

I and R *abbr* **1** initiative and referendum **2** intelligence and reconnaissance

I and S *abbr* **1** inspection and security **2** inspection and survey

¹ian·thi·na \ēˈan(t)thənə, īˈ-\ [NL, by alter.] *syn of* JANTHINA

²ianthina \"\ *n* -S **:** JANTHINA 2

ian·thine \ēˈan(t)thən, (ˈ)īˈa-\ *adj* [L *ianthinus* — more at IANTHINA] **:** having a violet color

ian·thin·i·dae \ˌīˌanˈthinəˌdē\ [NL, fr. *Ianthina,* type genus + -*idae*] *syn of* JANTHINIDAE

ian·thi·nite \ēˈan(t)thəˌnīt, īˈ-\ *n* -S [G *ianthinit,* fr. L *ianthinus* + G -*it* -ite] **:** a mineral $2UO_2.7H_2O$ consisting of a hydrous uranium dioxide and occurring as violet orthorhombic crystals

¹iao \(ˈ)ēˈaü\ *n* -S [Samoan] **:** WATTLEBIRD 1a

²iao \"\ *n* -S [native name in Hawaii] **:** a small silversides often used as bait in fishing

¹ia·pyg·ian \ˌīəˈpij(ē)ən\ *n* -S *usu cap* [*Iapygia,* ancient region in southeastern Italy (fr. L, fr. Gk) + E -*an*] **1 :** a member of one of several peoples anciently inhabiting the peninsula of Apulia in southeastern Italy **2 :** the language of the Iapygians

²iapygian \"\ *adj, usu cap* **:** of or relating to the Iapygians

ia·pyg·i·dae \ˌīəˈpijəˌdē\ [NL, fr. *Iapyg-, Iapyx,* type genus (alter. of *Japyg-, Japyx*) + -*idae*] *syn of* JAPYGIDAE

iarovize *var of* JAROVIZE

IAS *abbr* indicated airspeed

-iasis *pl of* -IA

ia·şi \ˈyäsh(ē)\ *or* ias·sy \ˈyäsē\ *adj, usu cap* [fr. *Iaşi* (*Jassy*), Romania] **:** of or from the city of Iasi, Romania **:** of the kind or style prevalent in Iasi

-i·a·sis \ˈīəsəs\ *n suffix, pl* -i·a·ses \-ˌsēz\ [NL, fr. L, fr. Gk, suffix of action, fr. verbs in -*ian,* -*iazein* (fr. nouns in -*ia* -y) + -*sis*] **:** morbid state or condition **:** disease having characteristics of (something specified) ⟨elephant*iasis*⟩ ⟨satyr*iasis*⟩ **:** disease produced by (something specified) ⟨ancylostom*iasis*⟩ ⟨habronem*iasis*⟩

ias·us \ēˈasəs, īˈ-\ [NL, fr. *Iasus, Iassus,* ancient city of Asia Minor] *syn of* JASUS

iat·mul \ˈyätˌmül\ *n, pl* iatmul *or* iatmuls *usu cap* **1 :** a Papuan people of the Sepik district, Territory of New Guinea **2 :** a member of the Iatmul people

iat·ric \(ˈ)īˈa·trik, -rēk\ *also* iat·ri·cal \-rəkəl, -rēk-\ *adj* [Gk *iatrikos,* fr. *iatros* healer, physician (fr. *iasthai* to heal) + -*ikos* -ic, -ical; perh. akin to L *ira* anger — more at IRE] **1 :** of or relating to a physician or medical treatment **:** MEDICAL ⟨outstanding ~ ability⟩ **2 :** MEDICINAL, HEALING, CURATIVE ⟨an extract with a remarkable ~ quality⟩

-i·at·ric \ēˈa·trik, -rēk\ *also* -i·at·ri·cal \-rəkəl, -rēk-\ *adj comb form* [-*iatric* fr. NL -*iatria* -iatry + E -*ic;* -*iatrical* fr. -*iatric* + -*al*] **:** of or relating to medical treatment **:** of or relating to healing ⟨hydr*iatric*⟩ ⟨psych*iatric*⟩

-i·at·rics \-ks\ *n pl comb form usu sing in constr* [-*iatric* + -*s*] **:** medical treatment **:** healing ⟨gyn*iatrics*⟩ ⟨ped*iatrics*⟩

-iatrist \ˈīə·trəst, ēˈa·trəst\ *n comb form* -S [-*iatry* + -*ist*] **:** physician **:** healer ⟨psych*iatrist*⟩ ⟨pod*iatrist*⟩

iatro- *comb form* [NL, fr. Gk, fr. *iatros* physician] **1 :** physician **:** medicine **:** healing ⟨*iatro*logy⟩ ⟨*iatro*genic⟩ **2 :** physician and ⟨*iatro*chemist⟩ **:** medicine or healing and ⟨*iatro*physics⟩ ⟨*iatro*-astrological⟩

iat·ro·chemical \īˌa·trō, ēˌ-+\ *adj* [*iatro-* + *chemical*] **:** of or relating to iatrochemistry **:** ¹CHEMICAL 1b

iat·ro·chemist \"+\ *n* [*iatro-* + *chemist*] **:** one believing in or practicing iatrochemistry

iat·ro·chemistry \"+\ *n* [*iatro-* + *chemistry*] **:** chemistry combined with medicine — used of the chemistry of the period about 1525–1660 dominated by the teachings of Paracelsus; compare IATROPHYSICS

iat·ro·gen·ic \īˌa·trōˈjenik, ēˌ-\ *adj* [*iatro-* + -*genic*] **:** induced by a physician — used chiefly of ailments induced in a patient by autosuggestion based on a physician's words or actions during examination — iat·ro·ge·nic·i·ty \=ˌ==jəˈnisəd·ē\ *n* -ES

iat·ro·mathematics \īˌa·trō, ēˌ-+\ *n pl but usu sing in constr* [NL *iatromathematica,* fr. *iatro-* + L *mathematica* mathematics, astrology; after Gk *iatromathēmatikos* one that practices medicine in conjunction with astrology — more at MATHEMATICS] **:** IATROPHYSICS

iat·ro·physicist \"+\ *n, archaic* **:** one who specializes in iatrophysics

iat·ro·physics \"+\ *n pl but usu sing in constr* [ISV *iatro-* + *physics*] **:** physics combined with medicine — used of a school of medicine of the 17th century that explained disease and the activities of the body in terms of physics rather than of chemistry; compare IATROCHEMISTRY

-i·a·try \ˈīə·trē, ēˈa·t-, -ri\ *n comb form* -ES [F -*iatrie,* fr. NL -*iatria,* fr. Gk *iatreia* art or action of healing, fr. *iatros* physician + -*eia* -y — more at IATRIC] **:** medical treatment **:** healing ⟨pod*iatry*⟩ ⟨gyn*iatry*⟩ ⟨psych*iatry*⟩

IAZ *abbr* inner artillery zone

ib *abbr* [L *ibidem*] in the same place

IB *abbr* **1** in bond **2** inbound **3** incendiary bomb **4** intelligence branch **5** invoice book

iba \ˈēbə\ *n* -S [Tag] **:** a medium-sized Philippine tree (*Cicca acida*) sometimes cultivated for its edible roundish greenish white fruit

IBA *abbr* indolebutyric acid

ibad \ˈēˌbad\ *n, pl* ibad *or* ibads *usu cap* **1 :** an Arab people in Hira between the Euphrates and the Arabian desert **2 :** a member of the Ibad people

iba·dan \ēˈbäd°n, -bad-\ *adj, usu cap* [fr. *Ibadan,* Nigeria] **:** of or from the city of Ibadan, Nigeria **:** of the kind or style prevalent in Ibadan

iba·dhi \əˈbädē\ *n, pl* ibadhi *or* ibadhis *usu cap* [after ʻAbdallah ibn-*Ibād*] **:** ¹IBADITE

¹iba·dite *also* aba·dite \əˈbäˌdīt\ *n* -S *usu cap* [ʻAbdallah ibn-*Ibād* (*Abād*), 7th cent. Arab religious leader + E -*ite*] **:** a member of an austere Muslim sect found chiefly in the northern part of Africa

²ibadite \"\ *n* -S *usu cap* [*Ibad* + -*ite*] **:** IBAD

iba·loi \ˈēbəˌlȯi\ *n, pl* ibaloi *or* ibalois *usu cap* **:** NABALOI

iban \(ˈ)ēˈbän\ *n, pl* iban *or* ibans *usu cap* **1 a :** a Dayak people of Sarawak, Borneo — called also *Sea Dayak* **b :** a member of such people **2 :** the Austronesian language of the Iban people

iba·nag \ˈēbəˌnäg\ *n, pl* ibanag *or* ibanags *usu cap* **1 a :** a people of northern Luzon inhabiting chiefly the Cagayan valley **b :** a member of such people **2 :** the Austronesian language of the Ibanag people

I bar *n, cap I* **:** a rolled iron or steel bar of I section used in construction work

I beam *n, cap I* **:** a rolled iron or steel beam or a cast steel beam of I section; *also* **:** a built-up beam of I section used esp. in structural ironwork (as in steel-framed buildings) — called also *I girder*

¹ibe·ri·an \īˈbirēən\ *n* -S *cap* [*Iberia,* ancient region of the Caucasus approximately equivalent to modern Georgia (fr. L *Iberia, Hiberia,* fr. Gk *Ibēria*) + E -*an*] **:** a member of one or more peoples anciently inhabiting the Caucasus in Asia between the Black and Caspian seas in the approximate region of the Soviet republic of Georgia and prob. being the ancestors of the Kartvelians

²iberian \(ˈ)=ˈ===\ *adj, usu cap* **:** of, relating to, or characteristic of Asiatic Iberia, its inhabitants, or their language **:** GEORGIAN

³iberian \=ˈ===\ *n* -S *cap* [*Iberia,* peninsula in southwestern Europe that contains Spain and Portugal (fr. L *Iberia, Hiberia,* fr. Gk *Ibēria*) + E -*an*] **1 a :** a member of one or more Caucasoid peoples anciently inhabiting the peninsula comprising Spain and Portugal and the Basque region about the Pyrenees, prob. being related in origin to the Mauretanians and other peoples of the northern part of Africa and early known to the Greeks and later conquered by the Romans, being short and dark and dolichocephalic, and being prob. the builders of the neolithic stone structures (as cairns, dolmens) found esp. in Spain and in the northern part of Africa and in France and Great Britain **b :** a native or inhabitant of Spain or Portugal or the Basque region about the Pyrenees **2 :** one or more of the languages natively spoken by the ancient Iberians

⁴iberian \(ˈ)=ˈ===\ *adj, usu cap* **:** of, relating to, or characteristic of the Iberian peninsula, its inhabitants, or their language ⟨tragedy and death are indeed recurrent themes in *Iberian* art —George Woodcock⟩

iberian tortoise *or* iberian turtle *n, usu cap I* **:** a common tortoise (*Clemmys leprosa* syn. *Testudo ibera*) of southwestern Europe and northern Africa

ibe·ric \(ˈ)īˈbirik, -ber-\ *adj, usu cap* [L *Ibericus, Hibericus,* fr. *Iberia, Hiberia* Iberia + -*icus* -ic] **:** IBERIAN

ibe·ris \īˈbirəs\ *n, cap* [NL, fr. L, peppergrass, fr. Gk *ibēris,* perh. fr. *Ibēria* (in Europe)] **:** a genus of Old World mostly glabrous plants (family Cruciferae) having entire or pinnatifid sometimes fleshy leaves and flowers with two long and two short petals succeeded by a broad ovate pod, the herbaceous members being often cultivated for their flat-topped clusters of white or purplish flowers — see CANDYTUFT

ibe·rite \ˈībəˌrīt, ˈībˌr-\ *n* -S [Sw or G *iberit,* fr. *Iberia* (in Europe), its locality + Sw or G -*it* -ite] **:** an alteration product of cordierite

ibero- *comb form, usu cap* [L *Iberus, Hiberus*] **:** Iberian **:** Iberian and ⟨*Ibero*-American⟩

ibero-romance \īˈbirō+\ *n, cap I&R* [*Ibero-* + *Romance*] **1 :** the Romance language of the Iberian peninsula prior to the emergence of Spanish, Portuguese, and Catalan as national languages **2 :** a language group of the Romance division consisting of Spanish, Portuguese, and Catalan

ibex \ˈīˌbeks\ *n* [L] **1** *pl* ibex *or* ibex·es **a :** one of several wild goats living chiefly in high mountain areas (as the Alps) of the Old World and having large recurved horns transversely ridged in front **b :** a wild goat (*Capra aegagrus*) now found in Asia Minor and supposed to be the progenitor of the domestic goat **c** (1) **:** MOUNTAIN GOAT (2) **:** MOUNTAIN SHEEP **2** *cap* [NL, fr. L] *in some classifications* **:** a genus that comprises the ibex and that is often considered a subgenus of *Capra*

IBI *abbr* invoice book, inwards

ibi·bio \ˌibəˈbē(ˌ)ō\ *n, pl* ibibio *or* ibibios *usu cap* **1 a :** a people of southeastern Nigeria **b :** a member of such people **2 :** the language of the Ibibio people, belonging to the Central branch of the Niger-Congo language family

ibid \ˈibəd\ *abbr* [L *ibidem*] in the same place

ibi·dem \ˈibəˌdem, -ˌdəm; əˈbīdəm, əˈbēd-, -ˌdem\ *adv* [L] **:** in the same place — usu. abbreviated and used (as in a footnote) to avoid repetition of source data (as author, title) in a reference immediately preceding; abbr. *ibid., ib.*

ibid·i·dae \īˈbidəˌdē\ [NL, fr. *Ibid-, Ibis,* genus of birds (fr. L *ibid-, ibis*) + -*idae*] *syn of* THRESKIORNITHIDAE

ibid·i·um \īˈbidēəm\ [NL, fr. L *ibid-, ibis* ibis + NL -*ium;* fr. the shape of the anthers] *syn of* SPIRANTHES

-ibility — see -ABILITY

ibis \ˈībəs *sometimes* ˈēb-\ *n, pl* ibis *or* ibis·es [L *ibid-, ibis,* fr. Gk *ibis,* fr. Egypt *hby*] **:** any of several wading birds related to the herons and constituting the family Threskiornithidae that inhabit warm regions in both hemispheres and feed on aquatic and amphibious animals and are distinguished by a long slender downwardly curved bill resembling a curlew's bill

ibisbill \ˈ==ˌ=\ *n* **:** a bluish gray bird (*Ibidorhyncha struthersii*) of central Asia having a long downcurved red bill and resembling a lapwing

-ible — see -ABLE

IBM *abbr or n* -S **:** an intercontinental ballistic missile

ibo \ˈē(ˌ)bō\ *or* ig·bo \ˈigˌbō\ *n, pl* ibo *or* ibos *or* igbo *or* igbos *usu cap* **1 a :** a Negro people of the country about the lower Niger **b :** a member of such people **2 :** a Kwa language of the Igbo people used as a language of trade and education in a large area of southern Nigeria

IBO *abbr* invoice book, outwards

ibo·ga·ine \əˈbōgəˌēn\ *n* -S [ISV *iboga* (fr. NL, specific epithet of *Tabernanthe iboga,* fr. a native name in central Africa) + -*ine*] **:** a crystalline alkaloid hallucinogen $C_{20}H_{26}N_2O$ obtained from the roots, bark, and leaves of an apocynaceous plant (*Tabernanthe iboga*) of equatorial Africa

ibo·li·um privet \īˈbōlēəm-\ *or* ibo·ta privet \īˈbōd·ə-\ *n* [*ibolium,* NL (specific epithet of *Ligustrum ibolium*), irreg. fr. Jap *ibota* wax tree + L *oleum* oil — more at OIL] **:** a privet (*Ligustrum ibolium*) produced by hybridizing two privets (*L. obtusifolium* and *L. ovalifolium*) that has pubescent branches and midribs of the under surfaces of the leaves and a glabrous calyx

ib·sen·i·an \(ˈ)ibˈsēnēən, (ˈ)ipˈ-, -sen-\ *adj, usu cap* [Henrik *Ibsen* †1906 Norw. poet and dramatist + E -*ian*] **:** of, relating to, or having the characteristics of the playwright Ibsen or his plays

ib·sen·ism \ˈibsəˌnizəm, ˈips-\ *n* -S *usu cap* [Henrik *Ibsen* + E -*ism*] **1 :** dramatic invention or construction characteristic of Ibsen whose plays attack conventional hypocrisies **2 :** adherence to or championship of Ibsen's plays and ideas

¹ib·sen·ite \-ˌnīt\ *n* -S *usu cap* [Henrik *Ibsen* + E -*ite*] **1 :** an admirer or devotee of Ibsen **2 :** a dramatist who imitates Ibsen's manner or technique

²ibsenite \"\ *adj, usu cap* **:** IBSENIAN

¹-ic \ik, ˌēk; ˌik *in a few words that have a heavy stress on a syllable preceding the penult, as "politic"*\ *adj suffix* [ME -*ik,* -*ic,* fr. OF & L; OF -*ique,* fr. L -*icus* — more at -Y] **1 :** having the character or form of **:** being ⟨panoram*ic*⟩ ⟨rhomb*ic*⟩ ⟨Samoyed*ic*⟩ **:** consisting of ⟨run*ic*⟩ **2 a :** of or relating to ⟨alderman*ic*⟩ ⟨datur*ic*⟩ ⟨Koran*ic*⟩ **b :** related to, derived from, or containing ⟨alcohol*ic*⟩ — esp. in names of acids and related compounds ⟨bor*ic*⟩ ⟨cinamm*ic*⟩ ⟨ole*ic*⟩ **3 :** in the manner of **;** like that of **:** characteristic of ⟨Byron*ic*⟩ ⟨quixot*ic*⟩ ⟨Puritan*ic*⟩ **4 :** associated or dealing with ⟨Ved*ic*⟩ **:** utilizing ⟨electron*ic*⟩ ⟨atom*ic*⟩ **5 :** characterized by **:** exhibiting ⟨nostalg*ic*⟩ **:** affected with ⟨allerg*ic*⟩ ⟨parapleg*ic*⟩ **6 :** caused by ⟨amoeb*ic*⟩ **7 :** tending to produce ⟨analges*ic*⟩ **8 :** having the highest valence of a (specified) element or a valence relatively higher than in compounds or ions named with an adjective ending in -*ous* ⟨ferr*ic* iron⟩ ⟨sulfur*ic* acid⟩ — compare ¹-ATE 2

²-ic \"\ *n suffix* -S [ME -*ik,* -*ic,* fr. OF & L; OF -*ique,* fr. L -*icus,* fr. -*icus* (adj. suffix)] **:** one having the character or nature of **:** one belonging to or associated with **:** one exhibiting or affected by ⟨glycon*ic*⟩ **:** one that produces ⟨ecbol*ic*⟩

IC *abbr* **1** immediate constituent **2** *often not cap* in charge **3** index correction **4** information center **5** information circular **6** inspected and condemned **7** interior communications **8** internal combustion **9** internal connection

ica \ˈēkə\ *n, pl* ica *or* icas *usu cap* [Sp, of AmerInd origin] **1 a :** a Chibchan people of northern Colombia **b :** a member of such people **2 :** the language of the Ica people

icac·i·na·ce·ae \iˌkasəˈnāsēˌē\ *n pl, cap* [NL, fr. *Icacina,* type genus (fr. ISV *icaco* + NL -*ina*) + -*aceae*] **:** a family of tropical chiefly woody plants of the order Sapindales with alternate leaves, panicled flowers, and drupaceous fruit — icac·i·na·ceous \=ˌ==ˈnāshəs\ *adj*

icaco \iˈkäˌkō, iˈkä-\ *or* icaco plum *also* hi·caco \(h)i-\ *n* -S [Sp *icaco, hicaco,* fr. Arawak] **:** COCO PLUM

-i·cal \ˈəkəl, ēk-\ *adj suffix* [ME, fr. LL -*icalis* (as in *clericalis* clerical, *grammaticalis* grammatical, *radicalis* radical) — more at CLERICAL, GRAMMATICAL, RADICAL] **:** -IC ⟨cosm*ical*⟩ ⟨fantast*ical*⟩ — sometimes differing from -*ic* in that adjectives formed with -*ical* have a wider or more transferred semantic range than corresponding adjectives in -*ic* ⟨econom*ical*: econom*ic*⟩ ⟨prophet*ical*: prophet*ic*⟩

¹icar·i·an \iˈka(a)rēən, (ˈ)īˈk-\ *adj, usu cap* [L *icarius* of Icarus (fr. Gk *Ikarios,* fr. *Ikaros* Icarus, Greek mythological character who flew so high on man-made wings that the sun melted them and sent him to destruction) + E -*an*] **:** of, relating to, or characteristic of Icarus: **a :** soaring too high for safety ⟨*Icarian* flight⟩ **b :** inadequate for or incapable of bringing about an ambitious project ⟨*Icarian* methods⟩

²icarian \"\ *adj, usu cap* [F *icarien,* fr. *Icarie,* communistic utopia in *Voyage en Icarie* (1842), novel by Étienne Cabet †1857 Fr. political radical (fr. *Icarie* Icaria, island in the Aegean sea) + F -*en* -an] **:** of, relating to, or constituting a communistic settlement established in the U.S. during the latter half of the 19th century by a group of French immigrants ⟨the last *Icarian* utopia . . . fizzled out in 1895 —*Time*⟩

³icarian \"\ *n* -S *usu cap* [F *icarien,* fr. *icarien,* adj.] **:** a member of an Icarian community

ICAS *abbr* intermittent commercial and amateur service

ICBM *abbr or n* -S **:** an intercontinental ballistic missile ⟨the ~ era —Clay Blair⟩

¹ice \ˈīs\ *n* -S *often attrib* [ME *is,* fr. OE *īs;* akin to OFris, OS, & OHG *īs* ice, ON *īss,* Av *isu-* icy, *aēxa-* cold, and perh. to Russ *inei* frost, Lith *ynis*] **1 a :** water reduced to the solid state by cooling and when pure constituting a nearly colorless brittle substance that in freezing expands about one eleventh in volume, that has a specific gravity of 0.9166 as compared with 1.0 for water at 4°C, that under normal atmospheric pressure is formed at and has a melting point of 0°C or 32°F, that occurs in the common form as hexagonal crystals, and that in large masses is classed as a rock — compare BLUE ICE, FROST, SNOW; HEAT OF FUSION **b :** the layer of frozen water covering a surface (as of a road, rink, or body of water) ⟨broke through the ~⟩ **:** the surface of a sheet of ice ⟨slipped on the ~⟩ ⟨skated down the ~⟩ ⟨an ~ carnival⟩ **2 :** the quality or state of being emotionally cold (as from formality, reserve, embarrassment, or hostility) ⟨perceptibly chilled by the ~ in his voice⟩ ⟨thawed a little of the ~ that held his lady's heart —Robert Murphy⟩ — compare BREAK THE ICE **3 :** a substance resembling ice in appearance or solid form ⟨these hydrogen ~s might well be retained in meteoritic particles —P.M.Millman⟩; *specif* **:** ICING **4 a :** a sweet frozen food containing a fruit juice or other flavoring and usu. served as a dessert or refreshment; *specif* **:** one containing no milk or cream (as a fruit ice or water ice) **b** *Brit* **:** a serving of ice cream; *specif* **:** ICE-CREAM CONE **5** *slang* **:** DIAMONDS ⟨fenced the ~ for the gang⟩; *broadly* **:** JEWELRY

Webster's Third New International Dictionary

OF THE ENGLISH LANGUAGE UNABRIDGED

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MERRIAM-WEBSTER INC., *Publishers*
SPRINGFIELD, MASSACHUSETTS, U.S.A.

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Library of Congress Cataloging in Publication Data
Main entry under title:

Webster's third new international dictionary of the English language, unabridged: a Merriam-Webster/editor in chief, Philip Babcock Gove and the Merriam-Webster editorial staff.
p. cm.
ISBN 0-87779-201-1

1. English language—Dictionaries. I. Gove, Philip Babcock, 1902–1972. II. Merriam-Webster, Inc.
PE1625.W36 1993
423–dc20 93-10630
CIP

MADE IN THE UNITED STATES OF AMERICA
484950QPH9796

evidence except in rebuttal ~ *vt* **1 a** : to give rest or repose to : refresh by repose ; lay or place at rest : allow to remain inactive, quiet, or undisturbed ⟨~*ed* his horse before starting up the grade⟩ ⟨you should ~ your eyes from so much reading⟩ **b** : to permit (as soldiers in ranks) to move, talk, and smoke while keeping one foot in place ⟨~*ed* his men between the drill exercises⟩ **2** : to set (as oneself) at rest ⟨~ yourself before the fire⟩ — often used formerly in greetings ⟨God ~ you merry, Sir —Shak.⟩ **3** : to place or lay on a support : support on or with something ⟨~ the book against the lamp⟩ ⟨~*ed* his gouty foot on a cushion⟩ **4 a** : to cause to be firmly fixed : GROUND ⟨was ~*ing* all his hopes on his son⟩ ⟨~*ed* her case on this argument⟩ **b** : to desist voluntarily from presenting evidence pertinent to (a case at law) **5** : to allow (land) to remain idle **syn** see BASE — **rest with** : to be the prerogative or province of ⟨any further investigation *rests with* the supervisor⟩

³**rest** \"\ *n* -s [ME, short for *arest* — more at ARREST] **1** *obs* : a checking or halting by or as if by arrest; *specif* : legal arrest **2** : a projection from or attachment on the side of the breastplate of medieval armor intended to support the butt of the lance **3** : CLARION 5

⁴**rest** \"\ *vt* [ME *resten*, short for *aresten* — more at ARREST] *chiefly dial* : ARREST

⁵**rest** \"\ *n* -s [ME, fr. MF *reste*, fr. *rester* to remain, rest] **1** : something that remains over: as **a rests** *pl* : REMAINS, RELICS **b** (1) *obs* : an amount still unpaid : a balance due (2) *Brit* : a reserve (as of a bank) consisting of profits remaining undivided after payment of dividends : SURPLUS **c** : the part remaining after removal of a part in fact or contemplation : all that is left : REMAINDER, RESIDUE — used with *the* ⟨if you will take the baby we can care for the ~⟩ ⟨used the ~ of the butter at breakfast⟩ **d** : a mass of surviving embryonic cells or of cells misplaced in development ⟨some neoplasms probably always arise from embryonic ~*s*⟩ ⟨adrenal *rests* in the kidney⟩ **2** : a series of repeated returns (as in a game of tennis) : a spell of uninterrupted returning — compare RALLY

⁶**rest** \"\ *vi* -ED/-ING/-S [ME *resten*, fr. MF *rester* to remain, be left over, fr. L *restare* to stand back, stop behind, be left over, fr. *re-* + *stare* to stand — more at STAND] **1** *obs* : to remain unpaid **2** : to be left over ; remain after something is taken away ; continue to exist

rest *abbr* restored

re·staff \(ˈ)rē+\ *vt* [*re-* + *staff*] : to provide with a new staff ⟨had to ~ the entire hotel⟩

re·stage \"+\ *vt* [*re-* + *stage*] : to present again or anew on the stage; *esp* : to present (as a play) with a new setting

re·stain \"+\ *vt* [*re-* + *stain*] : to stain again or anew; *esp* : to re-treat with a stain ⟨destaining and ~*ing* histological slides⟩

rest and residue *or* **rest, residue, and remainder** *n* [⁵*rest*] : the residuary estate of a testator

re·start \(ˈ)rē+\ *vb* [*re-* + *start*] *vt* **1** : to start again or anew ⟨~*ed* his car⟩ **2** : to resume (as an activity) after interruption ~ *vi* : to commence once more : resume operation

re·starter \"+\ *n* [*restart* + *-er*] : one that restarts; *esp* : a device for automatically restarting an apparatus or mechanism (as a phonograph)

re·state \"+\ *vt* [*re-* + *state*] : to state again or in a new form — **re·statement** \"+\ *n*

re·staur *or* **re·stor** \rəˈstȯ(ə)r\ *n* -s [*restaur* fr. F, alter. (influenced by *restaurer* to restore) of OF *restor* restoration, reparation; *restor*, alter. (influenced by *restore*) of *restaur* — more at RESTAURANT, RESTORE, n.] **1** : the legal recourse that insurers have against each other according to the date of their insurance **2** : the recourse of an insurer against the master of a ship if loss occurs through his negligence; *also* : the recourse of one against a guarantor or against one under obligation to indemnify

res·tau·rant \ˈrest(ə)rənt, -stə,ränt *also* -,stränt *or* -,stərnt\ *n* -s [F, food that restores, restaurant, fr. pres. part. of *restaurer* to restore, fr. L *restaurare* — more at RESTORE] : an establishment where refreshments or meals may be procured by the public : a public eating house

restaurant car *n*, *Brit* : DINING CAR

res·tau·rant·er \-ntə(r)\ *n* -s [*restaurant* + *-er*] : RESTAURATEUR

res·tau·ra·teur \ˌrestərəˈtər(-), ˌrȯ-, -ˈtü(ə)r\ *also* **res·tau·ran·teur** \ˌ-rän-ˈt- *also* ˌ-ran-\ *n* -s [*restaurateur* fr. F, fr. LL *restaurator* restorer, fr. L *restauratus* (past part. of *restaurare* to restore) + *-or*; *restauranteur*, modif. (influenced by *restaurant*) of F *restaurateur* — more at RESTORE] : the operator or proprietor of a restaurant

¹**res·tau·ra·tion** \ˌrestəˈrāshən, -eˌstȯˈr-\ *archaic var of* RESTORATION

²**res·tau·ra·tion** \restȯrȧsyōⁿ\ *n* -s [F, lit., restoral, restoration, fr. MF — more at RESTORATION] : RESTAURANT; *also* : the purveying of food (as by a restaurant)

res·tau·ra·tor \ˈrestəˌrād·ə(r)\ *n* -s [LL] *archaic* : RESTORER

res·tau·ra·trice \ˌrestərəˈtrēs\ *n* -s [F, fr. LL *restauratric-*, *restauratrix*, fem. of *restaurator* restorer — more at RESTAURATEUR] : a woman who operates or owns a restaurant

¹**restbalk** \ˈ-,-\ *n* [¹*rest* + *balk*] : a ridge of land between furrows

²**restbalk** \"\ *vt* : to leave restbalks in (land) in ploughing

rest cure *n* [¹*rest*] : treatment of disease (as neurasthenia or tuberculosis) by rest and isolation in a good hygienic environment

rest day *n* : a day which is set aside for rest or on which one departs from a normal or usual routine: as **a** (1) : SABBATH (2) : a day of equivalent religious import in religions other than Judaism and Christianity **b** : a day that is not a workday **c** : any of the days sometimes introduced into an open season on which hunting is not permitted

rested *past of* REST

re·steel \(ˈ)rē+\ *vt* [*re-* + *steel*] : to equip with or as if with new steel ⟨~*ed* himself to meet the challenge⟩

re·stem \"+\ *vt* [*re-* + *stem*] : to stem again ⟨a ship *restemming* its way⟩

rest·er \ˈrestə(r)\ *n* -s : one that rests

rest·ful \ˈrestfəl\ *adj*, *sometimes* **restfuller** \-fələ(r)\ *sometimes* **restfullest** \-fələst\ [ME, fr. ¹*rest* + *-ful*] **1** : marked by, affording, or suggesting rest and repose : offering freedom from toil, agitation, or effort ⟨something so beautiful and ~ about his method . . . so free from that fretful haste, that vehement striving —J.K.Jerome⟩ **2** : enjoying rest : being at ease : RELAXED, TRANQUIL, PLACID ⟨as if no . . . circumstances could put her for long together out of temper . . . her lips were full and ~ —Samuel Butler †1902⟩ **syn** see COMFORTABLE

rest·ful·ly \-fəlē, -li\ *adv* [ME, fr. *restful* + *-ly*] : in a restful manner or style : so as to be restful

rest·ful·ness *n* -ES [ME *restfulnes*, fr. *restful* + *-nes* -ness] : the quality or state of being restful

restharrow \ˈ-,-(,)-\ *n* [⁴*rest* + *harrow*] : a plant of the genus *Ononis*; *esp* : a European woody herb (*O. repens*) with pink flowers, unifoliolate leaves, and long tough roots

rest home *n* [¹*rest*] : an establishment for the care and housing of persons (as the aged, convalescents) that need special attention or services

rest house *n* **1** : a house or building for the rest and shelter of travelers; *specif* : a dak bungalow **2** : a resort facility (as a boarding house) featuring a quiet relaxing life and simple wholesome food and appealing esp. to a clientele seeking rest and relaxation

restie *obs var of* RESTY

restier *comparative of* RESTY

restiest *superlative of* RESTY

res·tiff *or* **res·tif** \ˈrestəf\ *adj* [ME *restif*, *restiffe* — more at RESTIVE] : RESTIVE 1c

res·ti·form body \ˈrestəˌfȯrm-\ *n* [L *restis* rope, cord + E *-iform* — more at RUSH] : either of a pair of prominent bands of nerve fibers on the dorsal surface of the medulla oblongata that form part of the lateral boundaries of the fourth ventricle and are continued upward as the inferior peduncles of the cerebellum

re·stimulate \(ˈ)rē+\ *vt* [*re-* + *stimulate*] : to reactivate by stimulation

resting *adj* [ME, fr. pres. part. of *resten* to rest, repose] **1** : not in growing condition : not physiologically active : DORMANT, QUIESCENT ⟨a ~ lily bulb⟩ ⟨~ nerve cells⟩; *also* : of, relating to, or marked by dormancy ⟨a ~ period⟩ ⟨~ stages⟩ **2** : not undergoing or marked by mitosis or other form of division though otherwise physiologically active ⟨a ~ stage⟩

resting cell *n* **1** : RESTING SPORE **2** : a living cell with a resting nucleus

resting egg *n* : WINTER EGG

resting nucleus *n* : a cell nucleus when not undergoing reproduction (as by mitosis)

resting-place \ˈ-,-\ *n* [ME, fr. *resting* (gerund of *resten* to rest, repose) + *place*] **1** : a place where rest may be taken **2** : the place where a dead person is laid **3** : a landing in a staircase : HALFPACE, QUARTERPACE

resting spore *n* [*resting*] : a spore (as many zygospores) that remains dormant for a period before germination and is usu. invested with a thickened cell wall to withstand adverse conditions (as of desiccation, heat, or cold) — see CHLAMYDOSPORE

resting wandering cell *n* : a fixed histiocyte of the loose connective tissue of the body

res·tio \ˈrestē,ō\ *n*, *cap* [NL, fr. L, maker of rope, fr. *restis* rope, cord — more at RUSH] : a large genus of leafless southern African and Australian herbs (family Restionaceae) having one-celled anthers and many-flowered spikelets with imbricated glumes — see CORDLEAF, ROPE GRASS

res·ti·o·na·ce·ae \ˌrestēəˈnāsēˌē\ *n pl*, *cap* [NL, fr. *Restion-*, *Restio*, type genus + *-aceae*] : a family of monocotyledonous herbs (order Xyridales) that resemble rushes and have either no leaves or tiny sheathing ones and glumaceous panicled flowers — **res·ti·o·na·ceous** \ˌ-ˈnāshəs\ *adj*

re·stipulation \(ˌ)rē+\ *n* [*re-* + *stipulation*] : an act of stipulating anew : RESTATEMENT

res·ti·tute \ˈrestəˌtüt, -stə-ˌtyüt\ *vb* -ED/-ING/-S [L *restitutus*, past part. of *restituere* to restore — more at RESTITUTION] *vt* **1** : to restore to a former state or position : REHABILITATE **2** : to give back : REFUND ~ *vi* : to become restored, rehabilitated, or refunded : undergo restitution

res·ti·tu·tio in in·te·grum \ˌrestəˈtüd·ē,ōˈnintəgrəm, -ˌō(ˌ)inin-ˈteg-\ *n* [LL] *Roman & civil law* : restoration to a whole or uninjured condition : restoration to the status quo ante

res·ti·tu·tion \ˌrestəˈtüshən, -stə-ˈtyü-\ *n* -s [ME, fr. OF, fr. L *restitution-*, *restitutio*, fr. *restitutus* (past part. of *restituere* to set up again, restore, fr. *re-* + *-stituere* — fr. *statuere*, to set up) + *-ion-*, *-io* -ion — more at STATUTE] **1** : an act of restoring or a condition of being restored: as **a** : restoration of something to its rightful owner : the making good of or giving an equivalent for some injury (as a loss of or damage to property) **b** : the final restoration of all things and persons to harmony with God's will **c** : restoration of a person to a former position or status; *also* : the condition of one so restored : REINSTATEMENT **d** : restoration of a thing or institution to its original state or form **e** *Brit* : restoration of conjugal rights **f** : a return to or recovery of a former physical state ⟨the ~ of an elastic body⟩ — compare COEFFICIENT OF RESTITUTION **2** : something intended to cause or serving to cause restoration of a previous state: as **a** (1) *Brit* : a legal action to compel resumption of cohabitation between a husband and wife who have separated that is now used only as preliminary to divorce (2) : an action based upon equitable principles to recover money or property that in good conscience belongs to the plaintiff or to prevent a defendant from being unjustly enriched at the expense of the plaintiff (3) : an action to restore the parties to a transaction that is being rescinded or avoided to the respective positions they occupied prior to entering into the transaction **b** : a movement of rotation that usu. occurs in childbirth after the head has been delivered and that causes it to point toward the side to which it was directed at the beginning of labor

res·ti·tu·tion·ism \-shəˌnizəm\ *n* -s [*restitution* + *-ism*] : RESTORATIONISM

res·ti·tu·tion·ist \-sh(ə)nəst\ *n* -s *often cap* [*restitution* + *-ist*] : one who holds some form of religious doctrine based on the belief that everything is ultimately to be restored to its pristine form and purity : RESTORATIONIST

restitution nucleus *n* : a cell nucleus that contains a diploid or double number of chromosomes and that results typically from failure of completion of a division in mitosis

res·ti·tu·tive \ˈrestəˌtüd·iv, -stəˌtyü-\ *adj* [ML *restitutivus*, fr. L *restitutus* (past part. of *restituere* to restore) + *-ivus* -ive — more at RESTITUTION] : constituting or tending toward restitution

res·ti·tu·to·ry \ˌrestəˈtüd·ərē, -stəˈtyü-; rəˈstichəˌtōrē\ *adj* [LL *restitutorius*, fr. L *restitutus* + *-orius* -ory] : of, relating to, or aiming at restitution

res·tive \ˈrestiv, -tēv *also* -təv\ *adj* [ME *restife*, *restiffe* stationary (of animals), refusing to go forward, resisting control, fr. MF *restif*, (fr. *rester* to remain, stop behind) + *-if* -ive — more at REST] **1** *archaic* **a** : disposed to rest : INACTIVE, SLUGGISH **b** : standing firm : unwilling to yield or adjust : PERSISTENT, STUBBORN, INFLEXIBLE **c** : stubbornly resisting control or guidance : obstinate in refusal : BALKY **2 a** *of a horse* : high-spirited and unwilling to submit to discipline or to stand at ease : FRACTIOUS **b** : marked by uneasiness and lack of quietness or attentive interest : FIDGETY ⟨a ~ crowd⟩ **syn** see CONTRARY

res·tive·ly \-təvlē, -li\ *adv* : in a restive manner

res·tive·ness \-tivnəs, -tēv- *also* -təv-\ *n* -ES : the quality or state of being restive

rest·less \ˈrestləs, *in rapid speech* -sl-\ *adj* [ME *restles*, fr. ¹*rest* + *-les* -less] **1 a** : deprived of rest or sleep : finding no rest : UNEASY ⟨the patient was ~ from pain⟩ **b** : not affording rest : UNRESTFUL ⟨a ~ night⟩ **2 a** : continuing without end : UNCEASING ⟨~ change⟩ **b** : moving or operating continuously : UNQUIET ⟨the ~ sea⟩ **3** : characterized by or manifesting unrest esp. of mind : lacking in repose : averse to inaction; *also* : CHANGEFUL, UNSETTLED, DISCONTENTED

restless cavy *n* : APEREA

restless flycatcher *n* : a small flycatcher (*Seisura inquieta*) of Australia that is steely blue above and white below and has the habit of hovering with the body arched and wings quivering

rest·less·ly *adv* : in a restless manner

rest·less·ness *n* -ES : the quality or state of being restless

rest mass *n* [¹*rest*] : the mass of a body exclusive of additional mass acquired by the body when in motion according to the theory of relativity

re·stock \(ˈ)rē+\ *vt* [*re-* + *stock*] : to stock again : provide new stock for ⟨~*ing* a forest with seedlings⟩ ⟨~*ed* the stream with trout⟩

restor *var of* RESTAUR

re·stor·able \rəˈstōrəbəl, -rēˈs-, -tȯr-\ *adj* [¹*restore* + *-able*] : fit for restoring or reclaiming; *esp* : capable of being rehabilitated ⟨~ prisoners⟩

re·stor·al \-ōrəl, -ȯrəl\ *n* -s [¹*restore* + *-al*] : RESTORATION

¹**res·to·ra·tion** \ˌrestəˈrāshən\ *n* -s [alter. (influenced by ¹*restore*) of ME *restauracion*, fr. MF or LL; MF *restauration*, fr. LL *restauration-*, *restauratio*, fr. L *restauratus* (past part. of *restaurare* to restore) + *-ion-*, *-io* -ion — more at RESTORE] **1** : an act of restoring or the condition or fact of being restored: as **a** : a bringing back to or putting back into a former position or condition : REINSTATEMENT, RENEWAL, REESTABLISHMENT ⟨the ~ of peace⟩ ⟨the ~ of the monarchy⟩ ⟨behold the different climes agree rejoicing in thy ~ —John Dryden⟩ **b** : a putting back into consciousness or health : recovery of health or strength ⟨~ from sickness⟩ **c** : the ultimate bringing of the whole universe including all men into harmony with the will of God — called also *final restoration* **d** : the act of giving back something to one deprived of it : RESTITUTION **e** : a putting back into an unimpaired or much improved condition ⟨the ~ of a painting⟩ **f** : the act or fact of replacing missing teeth or crowns or associated structures; *also* : the replacement (as a denture) used **g** : the reinstatement of the amount or penalty of a fidelity bond (as by a special payment) **2** : something that is restored; *specif* : a representation of the original form (as of a fossil animal or of a building) **3** : the process of putting a building back into nearly or quite the original form; *also* : the making of drawings or models or both designed to show the conceived original form of a building (as a ruin)

²**restoration** \"\ *adj*, *usu cap* : of, relating to, or constituting a period in English history often held to coincide with the reign of Charles II but sometimes considered to extend from his accession to that of Queen Anne ⟨*Restoration* drama⟩

res·to·ra·tion·er \ˌrestəˈrāsh(ə)nə(r)\ *n* -s [*restoration* + *-er*] : RESTORATIONIST

res·to·ra·tion·ism \-shəˌnizəm\ *n* -s [*restoration* + *-ism*] : the belief or doctrines of the restorationists

res·to·ra·tion·ist \-sh(ə)nəst\ *n* -s [*restoration* + *-ist*] **1** : one who believes in a temporary future punishment and a final restoration of all to the favor and presence of God **2** : one who makes restorations of buildings

restoration style *n*, *usu cap R* : an English style esp. of furniture and architecture characteristic of the period of the restoration of Charles II

¹**re·stor·ative** \rəˈstōrəd·iv, -tȯr-\ *adj* [ME *restoratif*, alter. (influenced by ¹*restore*) of *restauratif*, fr. MF, fr. L *restauratus* (past part. of *restaurare* to restore) + MF *-if* -ive — more at RESTORE] : of or relating to restoration : having power to restore — **re·stor·ative·ly** *adv* — **re·stor·ative·ness** *n* -ES

²**restorative** \"\ *n* -s [ME *restoratif*, fr. *restoratif*, adj.] : something (as a food or medicine) that serves to restore esp. a person to consciousness or rapidly to normal vigor

res·to·ra·tor \ˈrestəˌrād·ə(r)\ *n* -s [modif. (influenced by ¹*restore*) of F *restaurateur* — more at RESTAURATEUR] *archaic* : RESTAURATEUR; *also* : RESTAURANT

¹**re·store** \rəˈstō(ə)r, rēˈs-, -tȯ(ə)r, -tōə, -tȯ(ə)\ *vb* -ED/-ING/-S [ME *restoren*, fr. OF *restorer*, fr. L *restaurare* to put back into an original state, renew, fr. *re-* + *-staurare* (fr. *instaurare* to renew, restore, perform) — more at STORE] *vt* **1** : to give back (as something lost or taken away) : make restitution of : RETURN ⟨*restored* the lost child to its parents⟩ **2** : to put or bring back (as into existence or use) ⟨~ harmony among foes⟩ ⟨*restored* a city-manager plan of government⟩ **3** : to bring back to or put back into a former or original state : RENEW; *as* **a** : REBUILD, RECONSTRUCT **b** (1) : to put back into or replace in a former state of favor or grace : deliver from the consequences of sin (2) : to reinstate in a former position or office **c** : to bring back to a healthy state : cause to recover ⟨and his hand was *restored* whole as the other —Mk 3:5 (AV)⟩ **d** : to make calm or tranquil in mind **e** (1) : to bring back from a state of injury or decay or from a changed condition (as by repairing or retouching) : RENOVATE ⟨~ a painting⟩ (2) : to repair and alter (a building) with the aim of putting back into the original form ⟨~ a cathedral⟩ **f** : to form a picture or model of the original form of (as something lost or mutilated) : represent or reproduce in the original form ⟨~ ancient ruins⟩ **g** : to place in a text as conjecturally the original reading **4** : to bring (as a person) back to some former state ⟨*restored* the child to health⟩ : put again in possession of something ⟨~ the king to his throne⟩ **5 a** *obs* : to make amends or compensation for **b** *Scots law* : to give or make restitution to **c** *archaic* : to make good the loss or damage due to **d** : to put back into (a processed food) the original nutritive value by adding elements lost in processing or equivalents of such elements **6 a** : to put (itself) back into the original position or form ⟨an elastic body automatically ~*s* itself after deformation⟩ **b** : to bring (as steel damaged by overheating) back to normal condition **c** : to put back into a former or proper position ⟨*restored* the book to the shelf⟩ ~ *vi* **1** *obs* : RECOVER, REVIVE **2** : to restore a person or thing — **restore in blood** : to readmit to rights (as of a title or inheritance) forfeited under English law by attainder either of the person himself or of his ancestors — compare CORRUPTION OF BLOOD

²**restore** *n* -s [ME, fr. MF *restor*, fr. OF, fr. *restorer* to restore] *obs* : RESTORATION

restorement *n* -s [ME, fr. MF, fr. OF, fr. *restorer* to restore + *-ment*] *obs* : RESTORATION

re·stor·er \rəˈstōrə(r), rēˈs-, -tȯr-\ *n* -s [¹*restore* + *-er*] : one that restores or makes restorations

restoring force *or* **restoring torque** *n* [fr. pres. part. of ¹*restore*] : any one of the forces or torques that tend to restore a system or parts thereof to equilibrium after displacement

restoring moment *n* : RIGHTING MOMENT

restoritie *or* **restority** *n*, *pl* **restorities** [by alter.] *obs* : RESTORATIVE

re·stow \(ˈ)rēˈstō\ *vt* [*re-* + *stow*] : to stow (as freight) again or anew — **re·stow·al** \-ōəl\ *n* -s

rest period *n* [¹*rest*] **1** : a period when the internal condition of a wood plant is unfavorable for the growth of buds even though external conditions are favorable **2** : a period (as during winter or in a dry season) when bulbous plants lose their foliage and mature their bulbs

restr *abbr* restaurant

re·straighten \(ˈ)rē+\ *vt* [*re-* + *straighten*] : to straighten again or anew ⟨bent to ~ the seams of her hose⟩

re·strain \rəˈstrān, rēˈs-\ *vb* -ED/-ING/-S [ME *restreynen*, *restraynen*, fr. MF *restreindre*, *restraindre*, fr. L *restringere* to draw back tight, restrain, restrict, fr. *re-* + *stringere* to draw tight — more at STRAIN] *vt* **1 a** : to hold (as a person) back from some action, procedure, or course : prevent from doing something (as by physical or moral force or social pressure) ⟨~*ing* her charges . . . from overt acts of violence —C.H. Grandgent⟩ **b** : to limit or restrict to or in respect to a particular action or course : keep within bounds or under control ⟨~*ing* state banks which were inclined to do unsound business —*Dict. of Amer. Biog.*⟩ **2 a** : to moderate or limit the force, effect, development, or full exercise of : prevent or rule out excesses or extremes of ⟨~*ing* lax management⟩ **b** : to keep from being manifested or performed : REPRESS ⟨could hardly ~ her astonishment from being visible —Jane Austen⟩ **3** *obs* : to draw back (as a rein) tightly **4 a** : to deprive of liberty : place under arrest or restraint **b** : to deprive (as of liberty) by restraint : abridge the freedom of — used with *of* **5** *obs* : FORBEAR, FORBID ~ *vi* **1** *archaic* : REFRAIN **2** : to restrain a person or thing

syn CHECK, CURB, BRIDLE, SNAFFLE, INHIBIT: RESTRAIN is a general term suggesting use of force, pressure, or strenuous persuasion to hold back a person or thing from a course or action or to prevent the action itself ⟨Delaware, in commissioning its delegates, *restrained* them from assenting to any change in the "rule of suffrage" —E.K.Alden⟩ ⟨one wants to produce in the child the same respect for the garden that *restrains* the grown-ups from picking wantonly —Bertrand Russell⟩ RESTRAIN may also be used with any moderating action, any action that prevents extremes ⟨a law of 17 B.C. gave a legal position to slaves informally manumitted . . . but drastically *restrained* their power to acquire and bequeath property —John Buchan⟩ CHECK indicates a restraining of a course, activity, impetus, or effect; its suggestions may rest on uses of the word in horsemanship, chess, or military affairs ⟨if you, my dear father, will not take the trouble of *checking* her exuberant spirits . . . she will soon be beyond the reach of amendment —Jane Austen⟩ ⟨the ambition of churchmen to shine in worldly contests is disciplined and *checked* by the broader interests of the church —Henry Adams⟩ CURB, BRIDLE, and SNAFFLE likewise carry suggestions from horsemanship, CURB indicating drastic and quick checking, BRIDLE indicating a steady, continued guiding, controlling, holding from excess, and SNAFFLE indicating a light curbing ⟨control of money, bills, and the right of electing the councillors *curbed* somewhat the Governor's immense power —*Amer. Guide Series: Mass.*⟩ ⟨endowed . . . with zest, with abundance, with romping blood. She had never been *bridled* in mind or body —Francis Hackett⟩ ⟨whose potential violence of feeling is *bridled* by good form —*N.Y. Herald Tribune Bk. Rev.*⟩ INHIBIT, largely psychological or scientific in its suggestions, is likely to bring into consideration repressive or curbing effects of custom, morality, precept, or conscience ⟨the inherent immorality of the acts has become as strong an *inhibiting* factor as the fear of punishment —T.L.Karsten & J.H.Mathias⟩ ⟨a more and more courageous, a less and less *inhibited* medium of expression —F.B.Millett⟩

re·strain·able \-nəbəl\ *adj* : capable of being or subject to being restrained

re·strain·ably \-blē\ *adv* : in a restrainable manner

re·strained \-nd\ *adj* [fr. past part. of *restrain*] : marked by or manifesting restraint (as in art) : devoid of excess or extravagance : DISCIPLINED — **re·strain·ed·ly** \-n(ə)dlē, -li\ *adv* — **re·strain·ed·ness** \-nədnəs, -n(d)nəs\ *n* -ES

restrained beam *n* : a beam built in at the supports : an encastré beam

re·strain·er \-nə(r)\ *n* -s : one that restrains; *esp* : a chemical (as potassium bromide) used to retard the action of a photographic developer esp. on unexposed silver salts

restraining *adj* [fr. pres. part. of *restrain*] : used for restrain-

[redacted]